Neurocognitive Factors Underpinning Individual and Developmental Differences in Visual Short-Term Memory Capacity

Thesis (cumulative thesis)
Presented to the Faculty of Arts and Social Sciences
of the University of Zurich
for the Degree of Doctor of Philosophy

by

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Accepted in the Spring Term 2014
on the Recommendation of the Doctoral Committee:

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Zurich, 2014

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Acknowledgement

In this section, I want to acknowledge all the people who contributed to this work and supported me at different stages through my Ph.D. studies at the University Children's Hospital Zurich.

My first thank goes to my supervisor and mentor PD Dr. Peter Klaver who made this Ph.D. possible. I thank him for his excellent scientific mentoring, for all the inspiring discussions, for the constructive criticism of my work, and for sharing his view and expertise of memory and attention.

I next wish to express my gratefulness to Prof. Dr. med. Ernst Martin and PD Dr. Ruth Tuura for their valuable scientific and technical advice, and providing the required infrastructure and equipment for conducting the experiments at the University Children's Hospital Zurich. A lot of thank goes to Karoline Wurmitzer who worked on the same project as me, for her cordial and pleasant collaboration and not to forget, for her support during the peak periods of recruitment and data collection. I also want to thank all co-workers at the University Children's Hospital, especially Carmen Ghisleni and Steffen Bollmann for always offering their highly valuable IT advice, and Ursula Staubli for the organizational and administrative support. Thank you very much!

I would further like to thank Prof. Dr. Durk Talsma of the Ghent University and Prof. Dr. Guillén Fernández of the Donders Institute for their valuable advice and fruitful discussions.

My gratitude also goes to Prof. Dr. Dr. Andreas Maercker of the University of Zurich, who promoted my Ph.D. studies in the beginning, and for giving me the opportunity to complete this thesis.

Finally, my warmest thanks go to my family and Luise Mugrauer who always believed in me and without their support this thesis would not have been completed.

Summary

The way in which children and adults acquire knowledge about the world critically depends on the ability to temporarily process a limited amount of previously seen information in mind, typically referred to as visual short-term memory (VSTM) capacity. There is substantial evidence that neural activity in the posterior parietal cortex (PPC), which is a part of the fronto-parietal attentional network, predicts individual and developmental differences in VSTM capacity. This network alone, however, does not serve as a sufficient explanation for VSTM capacity variations. Instead, VSTM capacity may depend on additional neurocognitive factors such as limitations in relational binding abilities. To date, the extent to which these operations explain individual and developmental differences in VSTM capacity is largely unclear.

An important component of short-term relational memory is the processing of object-location associations. In the adult cognitive neuroscience literature, a growing body of evidence points to a role of the hippocampus in object-location processing. Alternatively, lesion studies have suggested that hippocampal structures are only involved in VSTM tasks when capacity limit had been exceeded, i.e., reflecting long-term memory functions. Furthermore, although several behavioral studies pointed to the importance of object-location processing during VSTM development, its neural substrates are still unknown.

The aim of the present thesis was to investigate the following questions: (1) whether neural activity in the hippocampus emerges below the individual VSTM capacity limit in adults, and (2) whether neural activity in the hippocampus and PPC differentially explain individual and developmental differences in VSTM capacity. Participants of three age groups (27 children, age 7-12 years; 19 adolescents, age 13-17 years; 21 adults, age 18-27 years) completed a delayed match-to-sample task that required encoding, maintenance, and retrieval of colored squares, spatially arranged within arrays of different set size conditions (1, 2, 4, and 6 squares).

The first study (**Study A**) focused on individual differences in VSTM capacity associated with hippocampal and parietal activity in the adult group (von Allmen, Wurmitzer, Martin, & Klaver, 2013). We found that neural activity in the hippocampus predicted individual VSTM capacity and emerged below individual VSTM capacity. Hippocampal

activity furthermore dropped when capacity limit had been exceeded. Neural activity in the PPC on the contrary increased with larger set size and leveled off beyond capacity limit. With this, we provide evidence for a hippocampus' contribution to VSTM capacity, which can be dissociated from neural activity in the PPC.

The second study (**Study B**) focused on individual differences in VSTM capacity associated with brain activity across the full developmental trajectory and on age-related increases in VSTM capacity (von Allmen, Wurmitzer, & Klaver, in press). Individual VSTM capacity was explained by neural activity in the hippocampus already by middle childhood. However, in children and adults, these effects were evident in different subregions along the longitudinal axis of the right hippocampus, suggesting that developmental increases in VSTM capacity relates to qualitative changes how object-location associations were processed. In contrast, neural activity in the right PPC was linearly correlated with age across the full developmental trajectory, suggesting quantitative changes in attention processing limitations.

Together, our findings provide new indications that individual and developmental differences in VSTM capacity can be explained by memory and attention processing limitations within an integrated neural network including the hippocampus and the PPC.

Zusammenfassung

Der Erwerb von Wissen im Kindes- und Erwachsenenalter wird insbesondere von der Kapazität des visuellen Kurzzeitgedächtnisses (engl. visual short-term memory; VSTM) mitbestimmt, in anderen Worten, wieviel visuelle Information unmittelbar verarbeitet werden kann. Es ist allgemein bekannt, dass neuronale Aktivität im posterioren parietalen Cortex (PPC) und die damit einhergehenden Aufmerksamkeitsprozesse individuelle und entwicklungsbedingte Unterschiede in der VSTM-Kapazität vorhersagen. Aufmerksamkeit allein dient jedoch nur bedingt als eine hinreichende Erklärung. Vielmehr werden diese individuellen und entwicklungsbedingten Unterschiede durch Aufmerksamkeits- sowie Gedächtnisprozesse bestimmt, wobei das Ausmass der gedächtnisbezogenen Beteiligung unklar ist.

Die assoziative Informationsverarbeitung ist in diesem Zusammenhang eine bedeutende Leistung des Gedächtnisses. Es gibt zunehmend Belege dafür, dass im Erwachsenenalter das Verarbeiten von Objekt und Ort (Objekt-Ort-Assoziation) vom Hippocampus unterstützt wird. Alternativ geht aus einigen Läsionsstudien hervor, dass hippocampale Strukturen erst nach der Überschreitung der VSTM-Kapazität mobilisiert werden, das heisst, wenn Langzeitgedächtnisprozesse zu tragen kommen werden. Ausserdem geht aus zahlreichen Verhaltensstudien hervor, dass insbesondere das Verarbeiten von Objekt-Ort-Assoziationen einer erheblichen Entwicklungsveränderung unterliegt, wobei deren neuronalen Substrate bislang unbekannt sind.

Ziel der vorliegenden Doktorarbeit war es die folgenden Fragen zu untersuchen: (1) ob neuronale Aktivität im Hippocampus ausdrücklich unterhalb der VSTM-Kapazitätsgrenze auftritt, dies sowohl im Erwachsenenalter als auch ab der mittleren Kindheit, und (2) ob neuronale Aktivität im Hippocampus und PPC in unterschiedlicher Weise individuelle und entwicklungsbedingte Kapazitätsunterschiede vorhersagen. Hierzu wurde mittels funktioneller Magnetresonanz-Tomographie die Hirnaktivität von 27 Kindern (7-12 Jahre), 19 Jugendlichen (13-17 Jahre), und 21 Erwachsenen (18-27 Jahre) gemessen, während dem diese sich mit einer visuell-räumlichen VSTM-Aufgabe beschäftigten. Diese Aufgabe erforderte das

kurz aufeinander folgende Enkodieren, Halten, und Abrufen von Objekt-Ort-Assoziationen unterschiedlicher Anzahl (1, 2, 4, oder 6 farbige Quadrate).

Die erste Studie (**Study A**) befasste sich mit individuellen Kapazitätsunterschieden im Erwachsenenalter und die damit in Verbindung stehende Aktivität im Hippocampus und PPC (von Allmen et al., 2013). Aus den Ergebnissen geht hervor, dass neuronale Aktivität im Hippocampus individuelle Unterschiede in der VSTM-Kapazität vorhersagt und unterhalb der individuellen Kapazitätsgrenze auftritt. Dabei haben wir einen hippocampalen Aktivitätsabfall beobachtet sobald die individuelle Kapazitätsgrenze überschritten wurde. Neuronale Aktivität im PPC hingegen stieg mit der Anzahl an der zu erinnernden Objekten an und flachte ab nachdem die individuelle Kapazitätsgrenze erreicht wurde. Hippocampale Aktivität wurde somit eindeutig VSTM-Prozessen zugeordnet und liess sich von neuronaler Aktivität im PPC abgrenzen.

Die zweite Studie (**Study B**) befasste sich mit individuellen Kapazitätsunterschieden über die Entwicklungsspanne und deren neuronalen Substrate (von Allmen, Wurmitzer, & Klaver, in press). Die Ergebnisse deuten auf eine hippocampale Beteiligung an VSTM-Prozessen hin, dies schon ab der mittleren Kindheit. Erwachsene und Kinder rekrutierten jedoch unterschiedliche Subregionen entlang der hippocampalen Längsachse was auf unterschiedliche Verarbeitungsmechanismen von Objekt-Ort-Assoziationen hinweist. Im Gegensatz zu diesen qualitativen Altersunterschieden im Hippocampus korrelierte die neuronale Aktivität im PPC linear mit Alter über die gesamte Altersspanne, was für einen quantitativen Entwicklungseffekt spricht.

Zusammenfassend zeigen die Resultate beider Studien, dass sich individuelle und entwicklungsbedingte Unterschiede in der VSTM-Kapazität durch unterschiedliche neuro-kognitive Faktoren erklären lassen, und zwar durch gedächtnisbezogene Verarbeitung im Hippocampus und aufmerksamkeitsbezogene Verarbeitung im PPC.

1. Introduction

Visual short-term memory (VSTM) is of enormous importance for humans to interact with a dynamically changing environment, in which the temporary storage and processing of previously seen information is essential to many cognitive tasks. Furthermore, it is well established that the amount of information that can be held in VSTM is highly limited. This is typically referred to as VSTM capacity, which differs greatly across individuals of the same age as well as over development (Conway, 2008; Gathercole, 1999; Pickering, Gathercole, Hall, & Lloyd, 2001). Since VSTM capacity is considered to be a significant predictor for individual differences in global fluid intelligence (Fukuda, Vogel, Mayr, & Awh, 2010), learning and academic achievements across development (Bull, Espy, & Wiebe, 2008; Gathercole, Pickering, Knight, & Stegmann, 2004), there has been a great deal of interest in the neurocognitive factors that underlie individual and developmental differences in VSTM capacity.

To date, the majority of memory and attention theories have associated VSTM capacity with individual and/or developmental differences in attention processing limitations and associated neural activity within attention networks including the posterior parietal cortex (PPC) (Bledowski, Rahm, & Rowe, 2009; Klingberg, Forssberg, & Westerberg, 2002; Klingberg, 2006; Magen, Emmanouil, McMains, Kastner, & Treisman, 2009; Vogel, McCollough, & Machizawa, 2005). A growing body of research, however, hints at the possibility that attention alone might not serve as a sufficient explanation for these capacity differences (Cowan, Morey, AuBuchon, Zwilling, & Gilchrist, 2010). Instead, VSTM capacity may depend on both attention and memory processing limitations. The extent to which memory operations explain individual and developmental differences in VSTM capacity is to date unclear. Within this framework, the hippocampus has been proposed to be involved in specific storage mechanisms for relational information which is highly debated.

The goal of the present thesis was to investigate whether neural activity in the hippocampus explains individual differences in VSTM capacity not only in adults but also by middle childhood, whether neural activity in the hippocampus and PPC differentially explain individual and developmental differences in VSTM capacity, and whether age related regional changes along the hippocampal longitudinal axis explain developmental increases in VSTM

capacity. For this purpose, we measured BOLD fMRI in three age groups (21 adults, age 18-27 years; 19 adolescents, age 13-17 years; and 27 children, age 7-12 years) while they performed a visuo-spatial change detection task.

But first, before reporting the experiments, let me briefly introduce the neural substrates of VSTM capacity, both in adults and across development. This section will be followed by an overview of the methodological considerations within our studies concerning the behavioral and neural measures of VSTM capacity. After the experimental part, a general discussion will bring this thesis to a conclusion.

2. Neural Substrates of VSTM Capacity

2.1. The Posterior Parietal Cortex and Attention

Along with the prefrontal cortex, one of the most acknowledged brain regions for being involved in VSTM functions is the PPC. There are, however, different accounts concerning its function within VSTM. One view emphasizes that the PPC constitutes a capacity limited storage system within VSTM. Neural activity in this region not only increased with the amount of to-be-held objects but leveled off when capacity limit had been exceeded (Todd & Marois, 2004; Vogel & Machizawa, 2004). Importantly, the asymptotic shape of activity across set size conditions was correlated with the behaviorally determined K-function (Cowan, 2001). The shape of this function assumes that our VSTM system is able to store visual information within a fixed number of slots irrespective of whether the actual amount of objects presented exceeds capacity limit (Fig. 2.1.). The asymptote indicates that capacity limit has been reached. However, one could argue that with larger set size, PPC activity is increased because a larger portion of attentional effort is demanded. An asymptotic shape could thereby also reflect the extent of attentional effort or control over storage space.

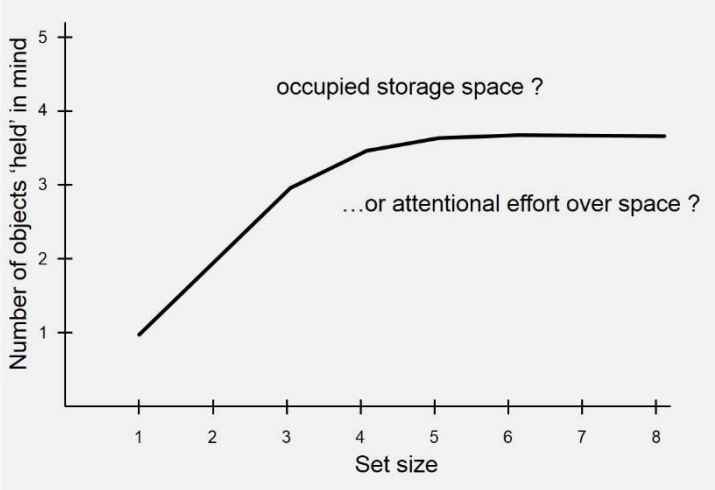

Figure 2.1. Number of objects held in mind as a function of set size (K-function). Does the asymptotic course reflect occupied storage space or control over space?

For example, Magen et al. (2009) probed VSTM related neural activity in the PPC with a similar change detection task as used by Todd and Marois (2004). Their most compelling result was that neural activity in the PPC disproportionately increased beyond the behaviorally determined capacity limit when the delay phase was extended from 1200 to 6000 ms. According to the author's rationale, extending the delay phase might have engaged more attentional rehearsal recourses in order to overcome a loss of information through decay or interference.

Further evidence that neural activity in the PPC reflects attention processes can be derived from accounts that probed VSTM under attentional distraction. In an exemplary study by Vogel and colleagues (2005), the amount of relevant information held in VSTM critically depended on individual differences in attentional filtering efficiency, i.e., the ability to exclude irrelevant objects from being represented in memory. This was measured by means of the contralateral delay activity (CDA) across lateral occipital and posterior parietal electrode sites. Individuals with higher VSTM capacity showed maximal CDA only for four items, whereas low-capacity individuals additionally showed maximal CDA for a condition in which two distractors had to be ignored among two target items (Fig. 2.2.).

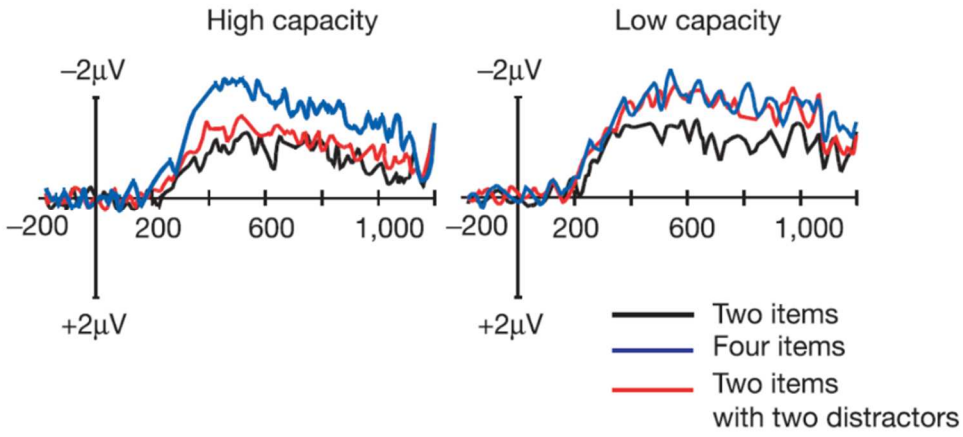

Figure 2.2. Contralateral Delay Activity (CDA) for high- and low-capacity individuals (Vogel et al., 2005).

2.2. Structural and Functional Changes Across Development

One of the most important contributions to maturational processes in the brain is the myelination of association fibers within and between cortical and subcortical regions. Especially in prefrontal and posterior parietal regions, white matter maturation is known to maintain relatively late even into early adulthood (Benes, 1989).

Current methods such as diffusion tensor imaging (DTI) provide powerful tools to examine developmental changes in prefrontal and parietal white matter connections. This method takes advantage of the fact that water in the white matter diffuses anisotropic which can be quantified as fractional anisotropy (FA). The FA value is thereby thought to provide a quantification of the white matter thickness. Using this method, Olesen et al. (2003) demonstrated developmental changes in prefrontal and parietal FA values in a population ranging from age 8 to 18 years. Specifically, in the superior frontal sulcus and inferior parietal lobe, these FA values correlated with increased VSTM-related neural activity in adjacent gray matter areas. The combination of DTI and fMRI in that study thus provided strong evidence that white matter maturation in the PPC parallels the functional development of VSTM. Another DTI study by Nagy et al. (2004) directly examined whether myelination was associated with developmental improvements in VSTM capacity. They found a positive correlation between developmental changes in FA values in the fronto-parietal network and increased VSTM capacity. Together, these studies have provided combined structural and functional evidence that myelination across development in the fronto-parietal network supports improved VSTM functions.

The functional consequences of maturational processes in the fronto-parietal network have been furthermore associated with improved attentional processing within VSTM. In this context, attentional filtering efficiency was employed to explain developmental increases in VSTM capacity (Olesen, Macoveanu, Tegnér, & Klingberg, 2007). Adults showed stronger neural activity in prefrontal and posterior parietal regions during maintenance compared to children. However, during attentional distraction only children showed neural activity in the prefrontal cortex.

2.3. VSTM Capacity: More than Attention

Although the idea that VSTM capacity is primarily constrained by attentional processing limitations is widespread, recent neurophysiological and behavioral accounts indicated that this factor might not be the sole explanation for capacity differences, at least not across development (Astle et al., 2014; Cowan et al., 2010). For example, younger children showed lower VSTM capacity compared to older children and adults, but their attentional filtering abilities were preserved when set size was held low (Cowan et al., 2010). In addition, several behavioral accounts indicate that object-location processing might as well explain developmental increases in VSTM capacity (Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Lorsbach & Reimer, 2005; Riggs, Simpson, & Potts, 2011; Simmering et al., 2009). Their neural substrates, however, are to date unknown. At this point, an important question can be raised, namely whether the hippocampus that has been associated with VSTM processing of relational information additionally explains individual and developmental differences in VSTM capacity.

2.4. The Hippocampus and Object-Location Processing

Traditionally, the hippocampus had been exclusively associated with long-term memory (LTM) processes (Cohen et al., 1999; Squire, Knowlton, & Musen, 1993). This view is primarily based on case reports that described severe deficits in LTM functions after the resection of bilateral hippocampus, but with seemingly intact short-term memory (STM) functions (Cave & Squire, 1992; Scoville & Milner, 1957). Together with other neuropsychological and behavioral evidence, these findings promoted the idea of two mutually exclusive memory systems (i.e., LTM and STM).

Several recent accounts, however, challenge this traditional view by proposing a hippocampus' role within a distributed neural network that also covers working memory. In an early study by Mitchell and colleagues (2000), younger, but not older, adults showed greater activity in the hippocampus during a working memory task in which they had to remember object-location associations. Because such effects were not evident during remembering of single features (i.e., either object or location), the authors concluded that age

related hippocampal dysfunction was specifically associated with deficits in working memory feature binding. In the following years, a series of fMRI and lesion studies corroborated the idea of a hippocampus' involvement in working memory, namely within the framework of VSTM object-location processing (Finke et al., 2008; Hannula & Ranganath, 2008; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Toepper et al., 2010). These findings raise serious doubts about a sharp dissociation between STM and LTM (see also Ranganath and Blumenfeld, 2005). Critical for the engagement of the hippocampus in memory might therefore not be the time interval between encoding and retrieval, but the character or type of relational information that is processed.

This alternative view, however, is far from being accepted by the wide scientific community. One major criticism is that hippocampal activity could in part depend on LTM processes during the completion of a VSTM task, even when the retention interval is brief (Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012). Using a standard change detection approach, Jeneson et al. (2012) showed that patients with hippocampal damage performed worse than controls only when set size exceeded capacity limit, suggesting that performance in that case depended on LTM processes. Indeed, since previous fMRI studies did not directly test whether hippocampal activity emerged below capacity limit, it still can be argued that hippocampal activity could have reflected LTM processes. An accurate evaluation of this controversy is therefore only possible once we distinguish between below-capacity and above-capacity related hippocampal activity.

In light of the development of subcortical structures, it was widely thought that maturational processes in the hippocampus reach an adult-like stage relatively early in development, i.e., already by middle childhood. However, a recent longitudinal study has found that subregions in the hippocampus may have different developmental trajectories even into early adulthood (Gogtay et al., 2006). Over time the total volume of the hippocampus remained constant, whereas the subregional volumes differed considerably. In particular, the posterior part of the hippocampus increased with age, while the anterior part decreased in volume. DeMaster and Ghetti (2013) furthermore found age related functional changes along the hippocampal axis associated with successful episodic retrieval of relational memories. That is, correct episodic retrieval of relational information in adults was associated with neural activity in the anterior hippocampus, whereas children showed the same pattern specifically

in the posterior hippocampus. Regional changes in the hippocampus were therefore suggested to contribute to developmental improvements in episodic retrieval.

3. General Aims and Questions

The goal of the present thesis was to evaluate whether the hippocampus supports memory related operations in the framework of VSTM. This question was investigated within an integrated neural network that also covers attention related processes associated with the PPC. To this end, functional MRI data were collected from three age groups (children, adolescents, and adults), while subjects completed a visuo-spatial change detection task.

First Question: Does neural activity in the hippocampus predict individual differences in VSTM capacity?

This question was investigated within **Study A** and **B**, i.e., in each of the three age groups. Given that the hippocampus supports successful VSTM object-location processing and based on behavioral studies of VSTM development, neural activity in this region is expected to predict individual VSTM capacity already by middle childhood. Most importantly, we aimed to test whether neural activity in the hippocampus emerged below the behaviorally determined VSTM capacity limit.

Second Question: Does neural activity in the hippocampus and PPC differentially explain individual and developmental differences in VSTM capacity?

This question was investigated within **Study A** and **B**, where the aim was to characterize the roles of the hippocampus and PPC within an integrated neural network supporting VSTM. Here, we asked two more questions: (1) Whether the hippocampus and PPC show differential activity patterns across set sizes, and (2) whether neural activity in these regions showed differential developmental trajectories.

4. Methodological Considerations

4.1. Behavioral Measures of VSTM Capacity

4.1.1. The Change Detection Approach

Ever since Phillips (1974) introduced the 'change detection' approach, it has evolved to a powerful method to probe the capacity of VSTM. Within a standard change detection (or 'delayed match-to-sample') paradigm, subjects have to compare two consecutive arrays of objects (sample and probe array) prior to a match/mismatch judgment. There are two versions of this approach: whole-display and single-probe recognition (Fig. 4.1.). In a whole-display recognition trial, the probe is either identical to the sample or differs in a feature (e.g., color) in one of the objects, i.e., a match/mismatch judgment has to be made upon the full set of objects. In a single-probe recognition trial, as it says, a single object is presented at probe at one of the studied locations, which is either old or new.

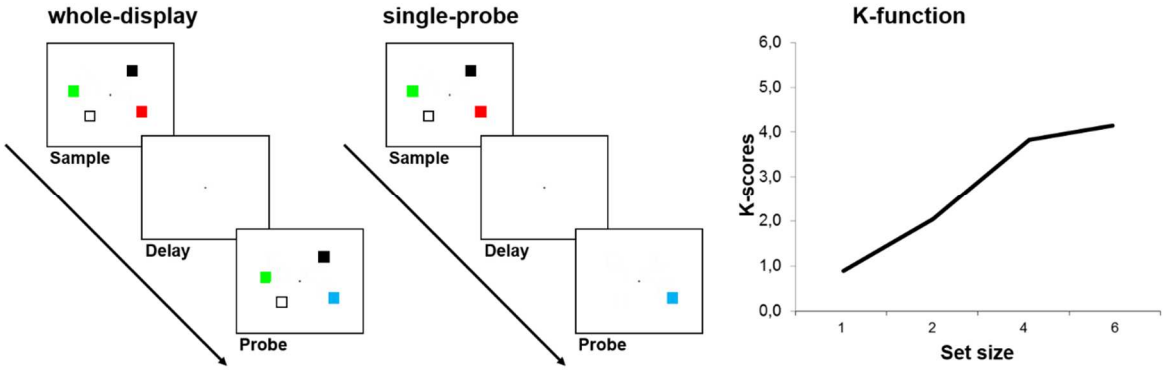

Figure 4.1. (left) Examples for change detection tasks. (right) Prototypical K-funtion for a capacity limit at around four objects.

The choice between whole-display or single-probe recognition depends on the problem under investigation. In order to probe the processing of object-location associations, it is advantageous to use the whole-display recognition version. This is because whole-display arrays selectively impair memory for relational binding information.

"…The presentation of a whole display of multiple items at test might require attention for the correct perception of this new set of objects. Thus resources needed to maintain the initial binding information would be diverted instead to perceive the multiple test items, making the original bindings held in memory "fall apart"…" (Wheeler & Treisman, 2002).

In order to probe VSTM object-location processing, we used a spatial version of the change detection approach (adapted from Luck and Vogel, 1997), in which colored squares were trial-by-trial pseudorandomly allocated at different locations. To keep measuring time as short as possible for the children, we refrained from extending the study protocol using further conditions which could have controlled for spatial, non-spatial associations, and single items. There is, however, supporting evidence that VSTM stores integrated representations of object features including their spatial locations (Bengson & Mangun, 2011; Klaver, Smid, & Heinze, 1999; Pertzov & Husain, 2013; Treisman & Zhang, 2006).

4.1.2. Estimating VSTM Capacity

Characteristic for most change detection approaches is the use of different set size conditions, i.e., the amount of to-be-held objects in the sample array. In order to estimate individual VSTM capacity, accuracy can then be assessed as a function of set size. This is usually conducted by the Cowan's K-formula (Cowan, 2001): K = (hit rate – false alarm rate) x N. The formula assumes that there is a likelihood of K/N on each trial that an observer correctly detects a change (K = capacity; N = set size). The consideration of the false alarm rate corrects K for guessing. Furthermore, it is assumed that an asymptotic shape of the so-called K-function indicates the upper limit of capacity (Fig. 4.1.), which can be determined by taking the maximal K-score across all set size conditions (K_{max}).

4.2. Neural Measures of VSTM Capacity

4.2.1. Basic Principles of Functional Magnetic Resonance Imaging

Within the last two decades, fMRI has become one of the most dominant research techniques for the study of human brain functions. This technique allows us to create images of the activated brain by measuring the hemodynamic response (Fig. 4.2.) to neural activity. The hemodynamic response consists of several phases. Initially, when neurons become active, there is a decrease in oxygenated hemoglobin due to the consumption of oxygen (initial dip). Thereafter, the vascular system supplies more oxygenated hemoglobin than is needed through an overcompensatory increase in cerebral blood flow (CBF) (Fox & Raichle, 1986). This leads to a decrease in the relative amount of deoxygenated hemoglobin. Because of the different magnetic properties of deoxygenated and oxygenated hemoglobin, the blood oxygenation level dependent (BOLD) contrast (Ogawa, Lee, Kay, & Tank, 1990) arises, which corresponds to an increase in the MR-signal. Finally, the BOLD signal decreases to a below-baseline level (post-stimulus undershoot) and returns back to baseline after the oversupply of oxygenated hemoglobin has been diminished.

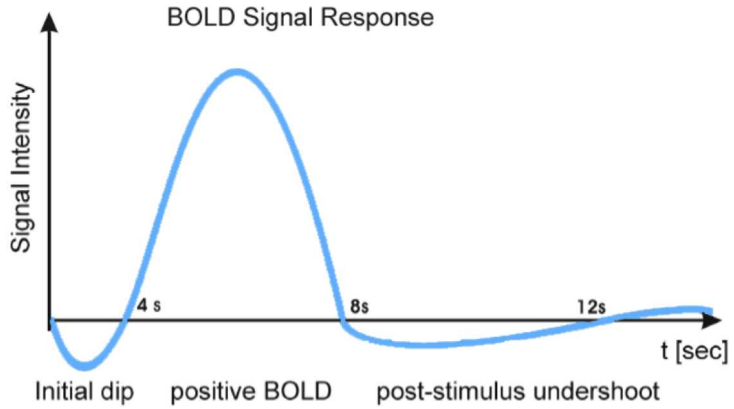

Figure 4.2. Time course of the hemodynamic response (Jäncke, 2005).

A major advantage of using fMRI is its non-invasiveness. In contrast to positron emission tomography (PET), which relies on the injection of radioactive tracers, fMRI can be repeated as many times as needed in the same individual. Another reason for using fMRI is its high spatial resolution of about 3 mm which allows a sharp localization of neural activity

even in subcortical regions such as the hippocampus. However, because the BOLD contrast is only observed about 3-8 seconds after stimulus onset, researchers using fMRI have to accept a lower temporal resolution as compared to for example electroencephalography (EEG). This can be especially challenging when the delineation of fast sequenced VSTM processes (i.e., encoding, maintenance, and retrieval) is aimed.

Another challenge concerns the fact that different timing of CBF in brain regions affects relative timing in BOLD signal. Numerous studies have shown that the HRF differs widely across the whole cortex as well as in adjacent voxels (Buckner et al., 1998; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000; Thomason, Burrows, Gabrieli, & Glover, 2005). With regard to the hippocampus, there is evidence of relatively poor vascular supply compared to other regions in the cerebral cortex (Borowsky & Collins, 1989). Specifically when examining hippocampal and posterior parietal regions, one should therefor consider to correct for these latency differences. This issue becomes primarily critical when attempting to quantify inter-regional correlations or causality which was not aimed within our studies.

4.2.2. Set Size Dependent Activation Patterns

In a previous study by Todd and Marois (2004), set size dependent brain activity was analyzed using K-weighted regressor coefficients. As mentioned above, K-scores show an asymptotic shape across set size conditions. It is for this reason, they exclusively found neural activity that increased with larger set size and leveled off when capacity limits had been reached. However, neural activity in different brain regions may differentially increase and/or decrease across set size conditions. One might hence overlook activation patterns such as for example an inverted U-shaped or drop function by examining neural activity by means of an underlying asymptotic function. We therefore modeled the hemodynamic response function for each of the set size conditions with regressors independent of K-measures.

On group level, whole-brain correction was used to initially review main effects of set size within and across the groups (i.e., performance and age groups). With respect to our regional specific hypothesis, small-volume correction and ROI analyses were applied to test for interactions between set size, performance and age groups. Most importantly, plotting group mean contrast values across set size conditions allowed us to characterize the

underlying functions (e.g., asymptotic or drop function) as well as variations in a function's shape across performance and age groups. Figure 4.3. exemplifies three possible alternatives for hippocampal activation patterns across set size conditions: An (1) asymptotic and (2) drop function would indicate a hippocampus' involvement below VSTM capacity limit, whereas an (3) expanding function would support the LTM argument. Within the ROI analyses in Study B, we additionally tested for linear relationships between individual K_{max}, age, and the activation difference between large (4 and 6) and small (1 and 2) set sizes. This approach allowed us to determine different set size dependent activation patterns across age and VSTM capacity using an individual differences approach.

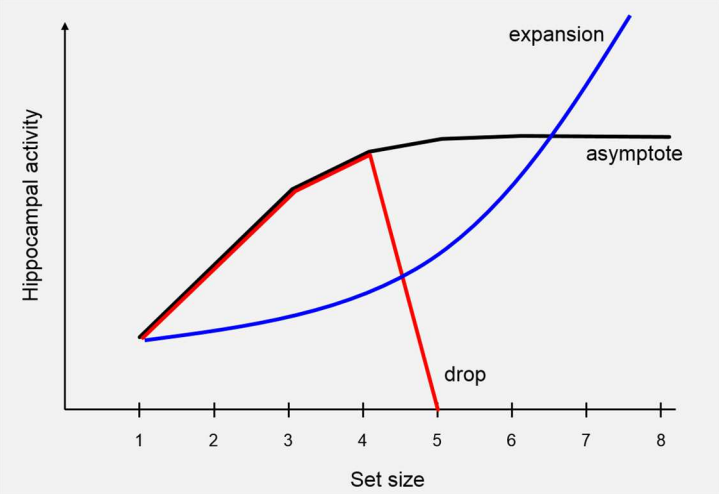

Figure 4.3. Hippocampal activity as a function of set size. At least three distinct activation pattern are possible: (1) Asymptote, (2) drop or inverted U-shape, or (3) expansion.

4.2.3. Regions of Interest Analyses

The definition of any Region of Interest (ROI) needs to be carried out prior to analyzing the dataset. As outlined in the introduction part, there is substantial reason to examine VSTM related neural activity specifically in the hippocampus and PPC.

A priori regions for the PPC were functionally defined as spheres with the center at coordinates reported by Todd and Marois (2004). The use of closely defined spheres seemed to be a reasonable approach since most anatomical atlases provide rather broad areas within the PPC. Furthermore, we decided to adopt the coordinates from Todd and Marois due to the content related proximity to their approach.

The hippocampal ROIs were anatomically defined as provided by the Automated Anatomical Labeling (AAL) atlas. In Study A, we treated the left/right hippocampus as two entire volumes. Based on previous studies that indicated structural and functional developmental changes along the hippocampal longitudinal axis, we decided to further divide the hippocampus into four subregions within Study B. In order to do that, we separated the hippocampal ROI at predefined Y-coordinates (DeMaster & Ghetti, 2013) into left/right head, anterior body, posterior body, and tail (Fig. 4.4.). Using these subregions, DeMaster and Ghetti (2013) found functional changes along the hippocampal axis associated with developmental improvements in episodic retrieval of relational information.

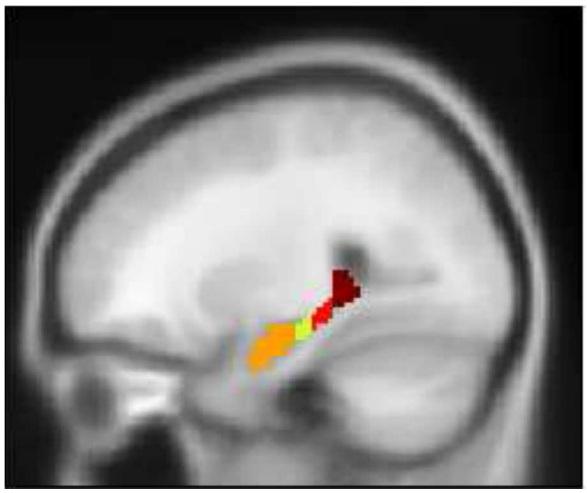

Figure 4.4. The hippocampal ROI containing of head, anterior body, posterior body, and tail. Obtained from the AAL atlas and subdivided according to predefined Y-coordinates (DeMaster & Ghetti, 2013).

4.2.4. Differences Between Children and Adults

Children and adults differ in many ways such as in the magnitude of movement during fMRI scanning, capacity for different levels in task difficulty, and emotional reactions during fMRI measurements. Task difficulty was calibrated through the piloting phase whereupon we agreed on a final version of the task that suited well adult and child capacity. It was thereby of particular interest to use only one version of the task to obtain comparability across age groups. In this context, we used only four set size conditions (1, 2, 4, and 6) that sufficiently differentiated between individuals across the age groups of interest. Timing parameters for encoding, maintenance, and retrieval were as well adjusted after the piloting phase. In particular, we prolonged the presentation time for the sample array from 200 to 800 ms and

discarded the presentation of a prior cue. Task instruction was conducted according to a standardized protocol. Each participant could thereafter practice until they felt ready for performing the task in the scanner. It should be mentioned that the training was based on trials that were not included in the actual task. During familiarization to the test environment and during the breaks between the scanning protocols, we paid attention to any obvious immoderate emotional reactions such as fear of the MR-measuring procedure. This was done to ensure a subject's well-being at any time during the measurement and to avoid emotional bias within our data. We instructed each participant with regard to avoiding immoderate head movements. To additionally minimize movement during the scanning session, we stabilized each participant's head with foam pillows. Within data preprocessing, we excluded participants with immoderate movement parameters and included additional movement regressors in the first-level analyses that additionally corrected for possible movement differences between age groups. Further consideration when analyzing fMRI data across development are with regard to age group specific normalization procedures. Within our studies spatial normalization was conducted using the standard MNI template for all participants.

5. Study A

Neural Activity in the Hippocampus Predicts Individual Visual Short-Term Memory Capacity

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Published in *Hippocampus*, 23(7), 606-615 (accepted 6 March, 2013)

5.1. Abstract

Although the hippocampus had been traditionally thought to be exclusively involved in long-term memory, recent studies raised controversial explanations why hippocampal activity emerged during short-term memory tasks. For example, it has been argued that long-term memory processes might contribute to performance within a short-term memory paradigm when memory capacity has been exceeded. It is still unclear, though, whether neural activity in the hippocampus predicts visual short-term memory (VSTM) performance. To investigate this question, we measured BOLD activity in 21 healthy adults (age range 19–27 yr, nine males) while they performed a change detection task requiring processing of object-location associations (delay period = 900 ms; set size conditions 1, 2, 4, and 6). Based on individual memory capacity (estimated by Cowan's K-formula), two performance groups were formed (high and low performers). Within whole brain analyses, we found a robust main effect of "set size" in the posterior parietal cortex (PPC). In line with a "set size x group" interaction in the hippocampus, a subsequent Finite Impulse Response (FIR) analysis revealed divergent hippocampal activation patterns between performance groups: Low performers (mean capacity = 3.63) elicited increased neural activity at set size two, followed by a drop in activity at set sizes four and six, whereas high performers (mean capacity = 5.19) showed an incremental activity increase with larger set size (maximal activation at set size six). Our data demonstrated that performance-related neural activity in the hippocampus emerged below capacity limit. In conclusion, we suggest that hippocampal activity reflected successful processing of object-location associations in VSTM. Neural activity in the PPC might have been involved in attentional updating.

5.2. Introduction

The hippocampus has long been thought to be exclusively involved in long-term memory processes (Scoville & Milner, 1957; Squire et al., 1993). Several studies, however, raised doubt on this traditional view by emphasizing its role within an integrated operational network that also covers short-term memory functions (Axmacher et al., 2007; Cabeza, Dolcos, Graham, & Nyberg, 2002; Finke et al., 2008; Hannula & Ranganath, 2008; Henke, 2010; Mitchell et al., 2000; Derek Evan Nee & Jonides, 2008, 2011; Olson et al., 2006; Piekema et al., 2006; Ranganath & D'Esposito, 2001; Schon, Hasselmo, LoPresti, Tricarico, & Stern, 2004; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). Critical for the engagement of the hippocampus in memory might be the character or type of relational information that is processed during memory operations (Henke, 2010). In that sense, the hippocampus might support object-location processing within visual short-term memory (VSTM). For example, Piekema et al. (2006) claimed that the hippocampus was involved in VSTM maintenance of spatial associations, i.e., maintenance of object-location associations revealed neural activity in the right hippocampus, whereas there was no hippocampal activity during maintenance of object-color associations or single items. Moreover, lesion studies indicated lower VSTM performance in patients with damaged hippocampus compared to healthy controls, when maintenance of spatial associations was required (Finke et al., 2008; Olson et al., 2006). An even earlier study showed that age-related hippocampal dysfunction was related to deficits in working memory feature binding (Mitchell et al., 2000). It has been argued, however, that hippocampal activity could in fact reflect long-term memory processes during the completion of a short-term memory task, that is, when memory capacity has been exceeded (Jeneson & Squire, 2012; Jeneson et al., 2012).

Here, we focus on the proposal that the hippocampus contributes to VSTM performance when object-location processing is required. Only few studies have investigated neural activity within the hippocampus in the prediction of individual short-term memory performance. In a recent intracranial EEG study, it has been claimed that short-term memory maintenance of multiple items was accompanied by precision of cross-frequency coupling in the hippocampus which predicted individual task performance (Axmacher et al., 2010). Such predictions of performance by hippocampal brain activity has not been shown in imaging

studies, possibly because a higher precision of coupling might not be automatically accompanied by an increase of brain activity (Fell et al., 2004).

More evidence support the role of the posterior parietal cortex (PPC) in VSTM performance (Todd & Marois, 2004, 2005; Xu & Chun, 2006). Todd and Marois (2004, 2005) have not only demonstrated that set size-related PPC activity levelled off when capacity limit had been exceeded, but also that neural activity in the PPC predicted individual VSTM capacity. These findings were interpreted as that the PPC embodies a storage system in the working memory framework. Further insight for a PPC's role in VSTM can be gained from unitary-store models, which describe short-term memory as a temporary activated part of long-term memory, and that attention limits the number of items that can be actively held (Jonides et al., 2008; McElree, 2006; Oberauer, 2002). Findings that PPC activity predicted individual storage capacity (Todd & Marois, 2004, 2005) might be interpreted alternatively: With larger set size, PPC activity is increased because a larger portion of attentional effort is demanded. Evidence for this alternative interpretation has been recently provided by fMRI studies proposing that the PPC is involved in maintaining attention toward to-be-held information, whereas the associative role of the hippocampus is not only thought to be supportive to short-term memory maintenance, but also to successful long-term memory formation (Nee & Jonides, 2008, 2011).

Taken together, there is a controversy about the hippocampus' involvement in VSTM (Finke et al., 2008; Jeneson & Squire, 2012; Jeneson et al., 2012; Olson et al., 2006; Piekema et al., 2006). It is unclear whether neural activity in the hippocampus predicts VSTM performance, that is, VSTM-related activity within the hippocampus has not yet been probed by taking into account individual memory capacity and varied set size conditions. Another important question is how to characterize the roles of the hippocampus and the PPC within a possible neural network supporting VSTM performance. Evidence suggests that the hippocampus is involved in the processing of object-location associations, and the PPC might be engaged in attentional updating of task relevant information. To investigate these questions, we measured a group of healthy subjects while they performed a simple VSTM change detection task (adapted from Luck and Vogel, 1997), in which accurate performance required encoding, maintenance and retrieval of colored squares, spatially arranged within arrays of different set size conditions. Similar tasks had been used in previous studies, which

showed that brain activity is modulated by the number of objects maintained in VSTM (Todd & Marois, 2004; Vogel & Machizawa, 2004), or that damaged hippocampus affected maintenance of spatial associations (Finke et al., 2008; Olson et al., 2006).

5.3. Material and Methods

5.3.1. Participants

Twenty-one healthy, paid subjects participated in the present experiment (mean age 22 yr, range 19–27, nine males, one left-handed). Written informed consent was obtained from all volunteers according to procedures approved by the Cantonal Ethics Committee Zurich. All participants were German speaking, had normal or corrected-to-normal vision, and had no history of neuropsychiatric disorders.

5.3.2. Task Design

The experiment was embedded within a developmental study including children aged 7 yr and older (not reported here). To keep MRI measuring time as short as possible, our VSTM task covered not more than four set size conditions (i.e., 1, 2, 4, and 6). We used colored squares as stimuli that were pseudorandomly assigned to nine different colors (red, green, yellow, blue, cyan, pink, black, white, and gray) and pseudorandomly allocated within a pre-defined field of view (as specified in Vogel and Machizawa, 2004). Each trial started with a central fixation cross on a light gray background (2000 ms). Subjects were instructed to retain a sample array (800 ms) over a short delay period (900 ms) and to make a match/mismatch decision to the presentation of a subsequent probe array (2000 ms; see Fig. 5.1., for an example). A mismatch was introduced by a change of color in one square, while stimulus locations were held constant within a trial. Responses were given with index fingers of the left and right hand. Left-right allocation of response types (match/mismatch) was counterbalanced across subjects. Eighty trials in four set size conditions (20 trials per set size condition, 50% matches) and 24 null events (3500 ms, fixation cross) were randomly intermixed over the entire scanning session. Each trial onset was jittered with a variable interstimulus interval (8 x 0 ms, 6 x 1000 ms, 4 x 2000 ms, and 2 x 3000 ms per set size condition).

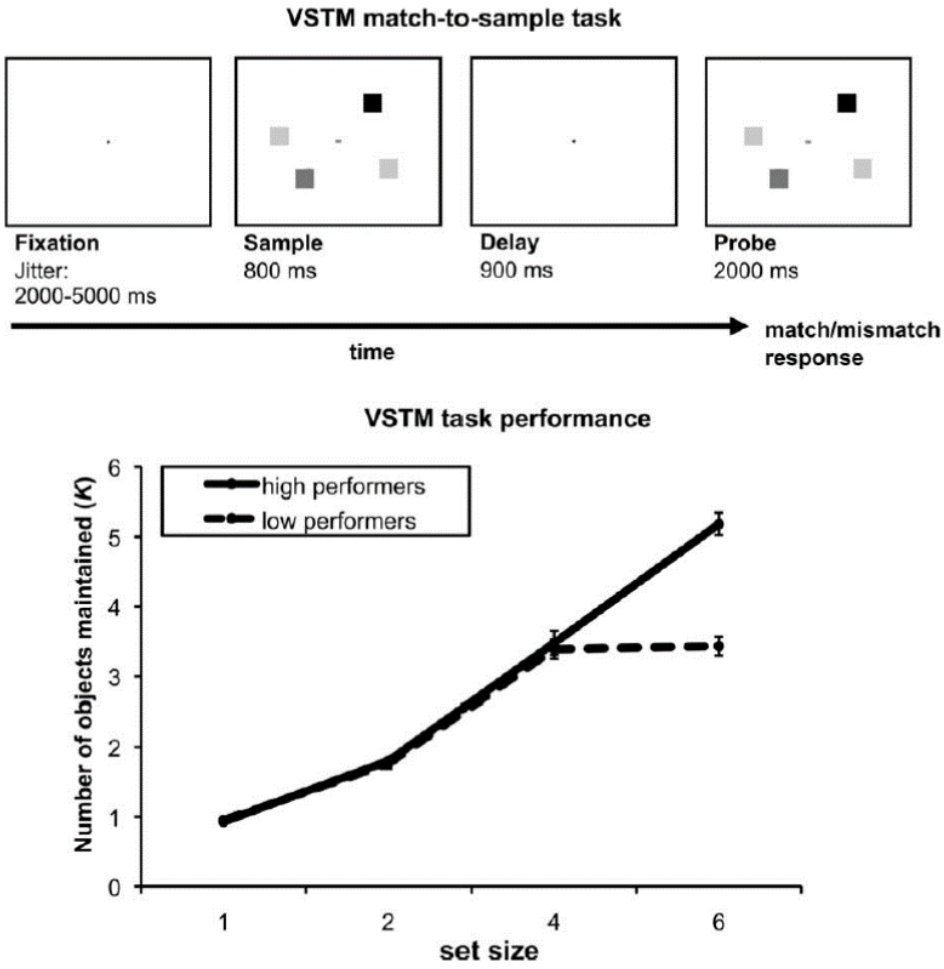

Figure 5.1. Example of the change detection task (mismatch trail). Participants were instructed to hold sample arrays consisting of one, two, four, or six colored squares for brief periods of time. By the presentation of the probe array, a match or mismatch response was required.

5.3.3. Image Acquisition

Whole brain functional images were acquired using conventional techniques on a 3-T GE MRI scanner (GE Medical Systems, Milwaukee, WI). Following four dummy scans, 354 T2*-weighted echo-planar imaging (EPI) scans were collected using an interleaved acquisition sequence (35 axial slices 15° to the AC-PC line, 4 mm thick, 3.13 x 3.13 mm2 in plane, TR = 1.9 s, TE = 32 ms, 75° flip-angle, matrix = 64 x 64, slice thickness = 3 mm, slice gap = 0.3 mm, FOV = 20 cm). For task presentation, we used a Dell Precision M70 laptop running with Presentation 11 (Neurobehavioral Systems, Albany, CA) for Windows. The stimuli were back-projected on a screen viewed by the subject through a prism mirror.

5.3.4. Behavioral Analysis

VSTM capacity was estimated by Cowan's K-formula (Cowan, 2001): K = (hit rate + correct rejection rate – 1) N, where N is the number of objects presented. Individual VSTM capacity was specified by taking the maximal K-score over all set size conditions (K_{max}). Two performance groups (high and low performers) were formed by means of a K_{max} median split. Statistical analyses were carried out using SPSS 20.0 for Windows (IBM, Armonk, NY). For both groups, estimated K-scores over all set size conditions were submitted to a repeated measures analysis of variance (rmANOVA). Greenhouse-Geisser correction was applied whenever assumptions of sphericity were violated.

5.3.5. Image Analysis

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London) running with MATLAB (R2011b; Mathworks, Natick, MA). All volumes were corrected for slice acquisition timing and realigned to the first image for motion correction using rigid body realignment. Then, imaging data were spatially normalized to the Montreal Neurological Institute (MNI) template brain (voxel size = 3 x 3 x 3) and spatially filtered with a 9 mm full-width half-maximum Gaussian kernel.

To obtain hemodynamic response at stimulus onset for each event type, a canonical hemodynamic response function (HRF; Friston et al., 1998) and its temporal derivative were modelled. The events of interest were locked to the onset of sample arrays and were convolved with a canonical hemodynamic response function (duration = 3700 ms; onset sample array until end probe array). Eight regressors were used to model neural response for the set size conditions (1, 2, 4, or 6) and probe types (match/mismatch). One additional regressor was used to model HRF related to incorrect trials (not considered in following statistical analyses) and additional six movement regressors were used to control for motion-correlated activity. Previous studies (e.g., Todd and Marois, 2004) used K-weighted regressor coefficients to predict individual set size-related activity. This approach seems to be appropriate to find neural activity that resembles an asymptotic function: With increasing set size, neural activity in certain brain regions (e.g., the PPC) initially increases and then tails off when individual

capacity limit has been reached. Our concern, however, was to test set size-dependent activity without an a priori assumption about the underlying function. By probing VSTM by means of an underlying asymptotic function, one might overlook brain regions which neural activity does not level off above capacity limit. For example, long-term memory accounts for the hippocampus (e.g., Jeneson and Squire, 2012) predict that neural activity would increase above capacity limit, while alternatively neural activity may decrease above capacity limit when information cannot be stored in short-term memory. It is for this reason, we performed first level analysis without K-weighted regressor coefficients. For the second level analysis, effects of interest were specified within a full factorial design (implemented in SPM8) with the factors "set size" (1, 2, 4, and 6), "probe" (match/mismatch), and "group" (high/low performers). Unequal variances were corrected for non-sphericity. Next, main effects and interactions were created by the linear combination of parameter estimates. Voxels were initially tested at a significance level of $p < .001$ (uncorrected; threshold > 10 voxels) and the reported clusters survived whole brain- or small volume correction (both FWE-corrected, $p < .05$). For small volume correction, a priori areas for the left and right hippocampus were defined in WFU Pickatlas (3.0.3) (Maldjian, Laurienti, Kraft, & Burdette, 2003) using the Automated Anatomical Labeling (AAL) atlas. A priori areas for the PPC were defined as spheres (radius = 5 mm) with the center at coordinates reported by Todd and Marois (2004) (left/right -22/23 -65/-59 42/45). WFU Pickatlas was also used to identify relevant anatomical landmarks, based on the AAL atlas.

To get an estimation of the time course of brain activity during sample, delay, and probe processing, we conducted a Finite Impulse Response (FIR) analysis with MarsBar toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). For the regions of interest (ROIs), we used the same a priori areas as defined within small volume correction. Time courses for each set size condition were extracted from the ROIs covering 13 temporal bins (each 1.9 s, starting at sample onset). Plots of time courses (averaged over all conditions) were initially used to detect peak activation. Next, percentage signal changes restricted to those time bins were fed into rmANOVAs for the left and right hippocampus and PPC, with the factors "set size" (1, 2, 4, and 6), "probe" (match/mismatch), and a between subjects factor of "group" (high/low performers). Main effects and interactions were calculated, and whenever a "set size x group" interaction was significant or showed a trend to significance, post hoc rmANOVAs

and paired comparisons were separately performed for high and low performers. To account for multiple comparisons, Bonferroni-corrections were applied. Greenhouse-Geisser correction was applied whenever assumptions of sphericity were violated.

5.4. Results

5.4.1. Behavioral Data

Within a rmANOVA, K-function showed a set size-dependent increase (main effect of "set size", $F(2.11, 40.0) = 394$, $p < .001$, $\eta_p^2 = 0.95$, $\varepsilon = 0.70$), which differed between high and low performers ("set size x group" interaction, $F(2.11, 40.0) = 31.1$, $p < .001$, $\eta_p^2 = 0.62$). Although high performers (mean $K_{max} = 5.19$, SD = 0.50) increased in K-scores up to set size six, low performers (mean $K_{max} = 3.63$, SD = 0.39) levelled off at set size four (Fig. 4.1.). In high performers, an additional post hoc rmANOVA showed a main effect of "set size", $F(2.06, 18.5) = 271$, $p < .001$, $\eta_p^2 = 0.97$, $\varepsilon = 0.69$, with significant mean K-score differences for the entire set of paired comparisons (all $p < .001$). Low performers also showed a significant main effect of "set size", $F(2.14, 21.4) = 140$, $p < .001$, $\eta_p^2 = 0.93$, $\varepsilon = 0.71$. As indicated by Figure 5.1., mean K-scores differed for all paired comparisons (all $p < .001$) except for the difference between set sizes four and six.

5.4.2. Imaging Data

Figure 5.2. illustrates different main effects of "set size" between high and low performers. In the low performers group, an increase in set size revealed neural activity in bilateral PPC and right hippocampus. High performers showed bilateral activity in the PPC in absence of hippocampal activation (Table 5.1.). A main effect of "set size" calculated over both performance groups showed neural activity in a variety of brain regions. These included parietal, occipital, temporal, and frontal regions. A subsequently conducted small volume correction (in the left and right hippocampus and PPC) revealed highly significant clusters in bilateral PPC, but not in the hippocampus. Most importantly, a "set size x group" interaction showed bilateral activity in the hippocampus. We did not find a reliable "set size x group" interaction in the PPC. Further, no significant activation was found for a main effect of "probe"

and for interactions with the factor "probe" ("set size x probe", "group x probe", and "set size x group x probe") in left and right hippocampus and PPC.

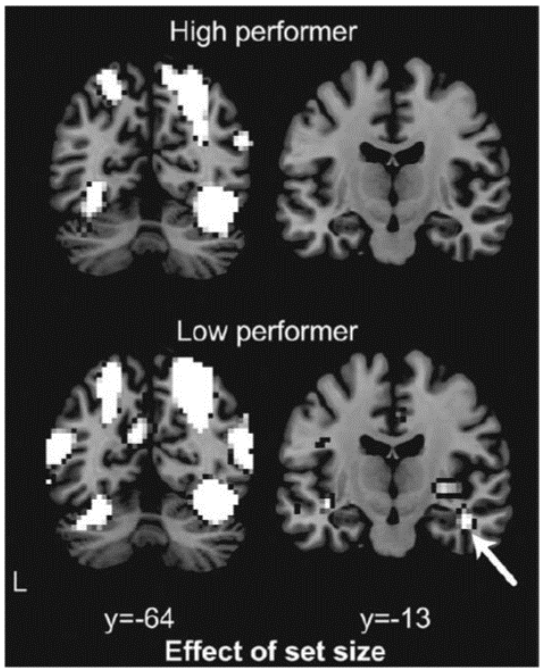

Figure 5.2. Neural activity within the whole brain analysis. (left) Main effects of 'set size', separately calculated for high and low performers, pointed to strong activity in the right PPC. (right) A main effect of 'set size' in the right hippocampus was only found in the group of low performers. Within these contrasts, a variety of other brain regions reached significance (see Table 1).

Table 5.1. Statistical results of the whole brain analysis (high and low performers)

	Brain region	**X**	**Y**	**Z**	**z-value**	***p-value***
Main effect of 'SET SIZE'						
Whole brain correction (HP)	Left middle occipital gyrus	-27	-88	13	Inf	0.000
	Right middle occipital gyrus	33	-91	13	Inf	0.000
		54	-70	25	4.61	0.028
	Right superior parietal lobe	27	-61	49	Inf	0.000
	Right inferior orbito-frontal gyrus	30	23	-8	6.18	0.000
	Right superior medial frontal gyrus	6	26	43	6.11	0.000
	Left superior medial frontal gyrus	-6	26	40	6.09	0.000
	Right anterior cingulum	6	38	22	4.61	0.029
	Left insula	-33	20	-11	5.58	0.000
	Left superior parietal lobe	-18	-70	55	4.95	0.006
		-27	-61	58	4.79	0.013
		-24	-58	49	4.76	0.015
	Left inferior parietal lobe	-39	-79	43	4.77	0.014
	Right supramarginal gyrus	69	-28	28	4.75	0.015

SVC (HP)	Left PPC	-21	-64	46	3.62	0.001
	Right PPC	27	-61	46	7.58	0.000
Whole brain correction (LP)	Right middle occipital gyrus	33	-88	10	Inf	0.000
	Right superior parietal lobe	27	-67	49	Inf	0.000
	Right inferior occipital gyrus	42	-64	-17	6.97	0.000
	Right inferior frontal gyrus, pars opercularis	48	8	25	7.79	0.000
	Left middle occipital gyrus	-33	-94	13	7.30	0.000
	Left superior parietal lobe	-24	-61	55	6.15	0.000
	Left inferior occipital gyrus	-24	-85	-8	5.52	0.000
	Right superior medial frontal gyrus	6	26	43	6.88	0.000
	Right insula	30	23	-5	6.72	0.000
	Right middle temporal gyrus	66	-43	10	5.88	0.000
	Right supramarginal gyrus	69	-28	28	5.62	0.000
		54	-31	25	5.45	0.001
	Right inferior frontal gyrus, pars triangularis	45	38	25	5.72	0.000
	Left middle temporal gyrus	-57	-64	16	5.48	0.001
	Left supramarginal gyrus	-57	-25	22	5.44	0.001
	NA	-48	-76	28	5.40	0.001
	Right middle cingulum	9	-28	46	5.42	0.001
		12	-46	34	5.15	0.003
	Left posterior cingulum	-6	-43	31	5.39	0.001
	Left insula	-30	26	-8	5.42	0.001
	Left precentral gyrus	-39	2	31	5.18	0.002
	Left middle frontal gyrus	-24	29	43	5.11	0.003
	Right middle frontal gyrus	33	2	61	4.79	0.000
SVC (LP)	Right hippocampus	39	-13	-20	3.55	0.017
	Left PPC	-24	-64	46	4.91	0.000
		-24	-64	37	4.53	0.000
	Right PPC	27	-61	46	Inf	0.000
'SET SIZE x GROUP' interaction						
SVC	Left hippocampus	-36	-16	-17	3.39	0.027
	Right hippocampus	39	-13	-23	3.64	0.012

Main effects and interactions for high performers (HP) and low performers (LP) are listed after whole brain- or small volume correction (SVC), both corrected for multiple comparisons (FWE, $p < .05$, threshold > 10 voxels). Significant voxels are listed in MNI standard space (X/Y/Z). Voxels not found by the AAL atlas are indicated as "NA".

As shown in Figure 5.3., FIR analyses showed peak activation at time bin four for the left and right hippocampus. At this time bin, high performers showed a steady increase in activity with larger set sizes, whereas low performers showed maximal activity at set size two and reduced activity at larger set sizes. A following rmANOVA revealed no main effects of "set size" in bilateral hippocampus (left hippocampus, $F(3, 57) = 0.47$, $p = .71$, $\eta_p^2 = 0.024$, and right hippocampus, $F(3, 57) = 1.09$, $p = .36$, $\eta_p^2 = 0.05$). The observation of different set size-related activation patterns between the performance groups (Fig. 5.3.) was supported by a significant "set size x group" interaction in the right hippocampus and a trend to significance in the left hippocampus (right hippocampus, $F(3, 57) = 4.44$, $p = .007$, $\eta_p^2 = 0.19$, and left hippocampus, $F(3, 57) = 2.55$, $p = .065$, $\eta_p^2 = 0.12$). A post hoc rmANOVA within the right hippocampus revealed a main effect of "set size" only in the group of low performers (low performers, $F(3, 30) = 3.64$, $p = .024$, $\eta_p^2 = 0.27$, and high performers, $F(3, 27) = 2.29$, $p = .10$, $\eta_p^2 = 0.20$). They showed increased neural activity at set size two compared to set size six ($p = .024$). In the left hippocampus, main effects of "set size" were not significant in both groups (high performers, $F(3, 27) = 1.85$, $p = .16$, $\eta_p^2 = 0.17$, and low performers, $F(3, 30) = 1.10$, $p = .36$, $\eta_p^2 = 0.10$). Paired comparisons showed significantly increased neural activity only in high performers at set size six compared to set size two ($p = .017$). A main effect of "probe" and the remaining interactions (i.e., "set size x probe", "group x probe", and "set size x group x probe") were nonsignificant.

Time courses for the PPC pointed to maximal neural activity at time bins three and four (Fig. 5.3.). Consequently, averaged percentage signal changes of these two time bins were used to perform the FIR analyses within the left and right PPC. Figure 5.3. shows a bilateral increase in PPC activity with larger set size in both groups. In line with this, a rmANOVA showed a main effect of "set size" in the left PPC, $F(1.81, 34.4) = 7.66$, $p = .002$, $\eta_p^2 = 0.29$, $\varepsilon = 0.60$, and in the right PPC, $F(1.68, 31.9) = 25.3$, $p < .001$, $\eta_p^2 = 0.57$, $\varepsilon = 0.56$. Because there was no evidence for a "set size x group" interaction in the PPC (left PPC, $F(1.81, 34.4) = 0.73$, $p = .48$, $\eta_p^2 = 0.04$, $\varepsilon = 0.60$, and right PPC, $F(1.68, 31.9) = 0.88$, $p = .41$, $\eta_p^2 = 0.04$, $\varepsilon = 0.56$), we forewent post hoc rmANOVAs for this region.

In addition, a "set size x probe" interaction reached significance in the left and right PPC (left PPC, $F(3, 57) = 4.29$, $p = .008$, $\eta_p^2 = 0.18$, and right PPC, $F(3, 57) = 2.85$, $p = .045$, $\eta_p^2 = 0.13$). For a main effect of "probe" and the remaining interactions (i.e., "set size x probe" and

"set size x group x probe"), no significant activations were found. Because PPC analyses were calculated with averaged time bins (i.e., time bin 3 and 4), this could have yield higher statistical power compared to the FIR analyses performed within the hippocampus (which included measures of a single time bin 4). To take account of this incongruity, we separately performed two FIR analyses within the PPC for two single time bins (i.e., time bin 3 and 4). This emerged no marked changes compared to the reported results except for a significant main effect of "probe" in the left PPC at time bin 4, $F(1, 19) = 5.86$, $p = .026$, $\eta_p^2 = 0.24$.

We further probed set size dependent activity within an individual differences approach. First we computed t-contrasts $S_{max} > S1$ in a whole brain analysis (S_{max} = highest reached set size level, S1 = set size 1) at the first level. This captured increases in neural activity between set size one and the largest number of objects successfully processed for each participant. A subsequent one-sample t-test on the group level (N = 21) revealed neural activity in both the hippocampus and PPC (Table 5.2.). As time course analyses indicated that neural activity in the hippocampus collapsed above capacity-limit, we computed individual contrasts $S_{max} > S6$ (S6 = set size 6). This tested for neural activity differences when capacity limit had been exceeded. In line with the FIR analyses, a one-sample t-test (N = 20; excluding one subject who had a K_{max} of 6) revealed neural activity in the hippocampus, but not in the PPC.

Table 5.2. Statistical results of the whole brain analysis (individual differences)

	Brain region	**X**	**Y**	**Z**	**z-value**	***p-value***
'S_{max} > S1'						
Whole brain correction	Right middle occipital gyrus	30	-91	19	5.06	0.006
		39	-91	10	5.06	0.006
	Right fusiform gyrus	24	-79	-11	4.92	0.011
SVC	Right hippocampus	33	-22	-14	3.44	0.022
	Left PPC	-24	-64	37	3.89	0.001
		-21	-64	46	3.60	0.002
	Right PPC	27	-61	46	4.38	0.000
'S_{max} > S6'						
Whole brain correction	Right pallidum	24	-10	-5	5.32	0.003
	Right inferior temporal lobe	48	-4	-32	5.02	0.010
	Right postcentral gyrus	21	-34	64	4.92	0.015

SVC	Right hippocampus	36	-22	-8	3.75	0.010
		39	-13	-14	3.62	0.015
		27	-10	-26	3.41	0.029

One-sample t-tests are listed after whole brain- or small volume correction (SVC), both corrected for multiple comparisons (FWE, $p < .05$, threshold > 10 voxels). Significant voxels are listed in MNI standard space (X/Y/Z). Voxels not found by the AAL atlas are indicated as "NA".

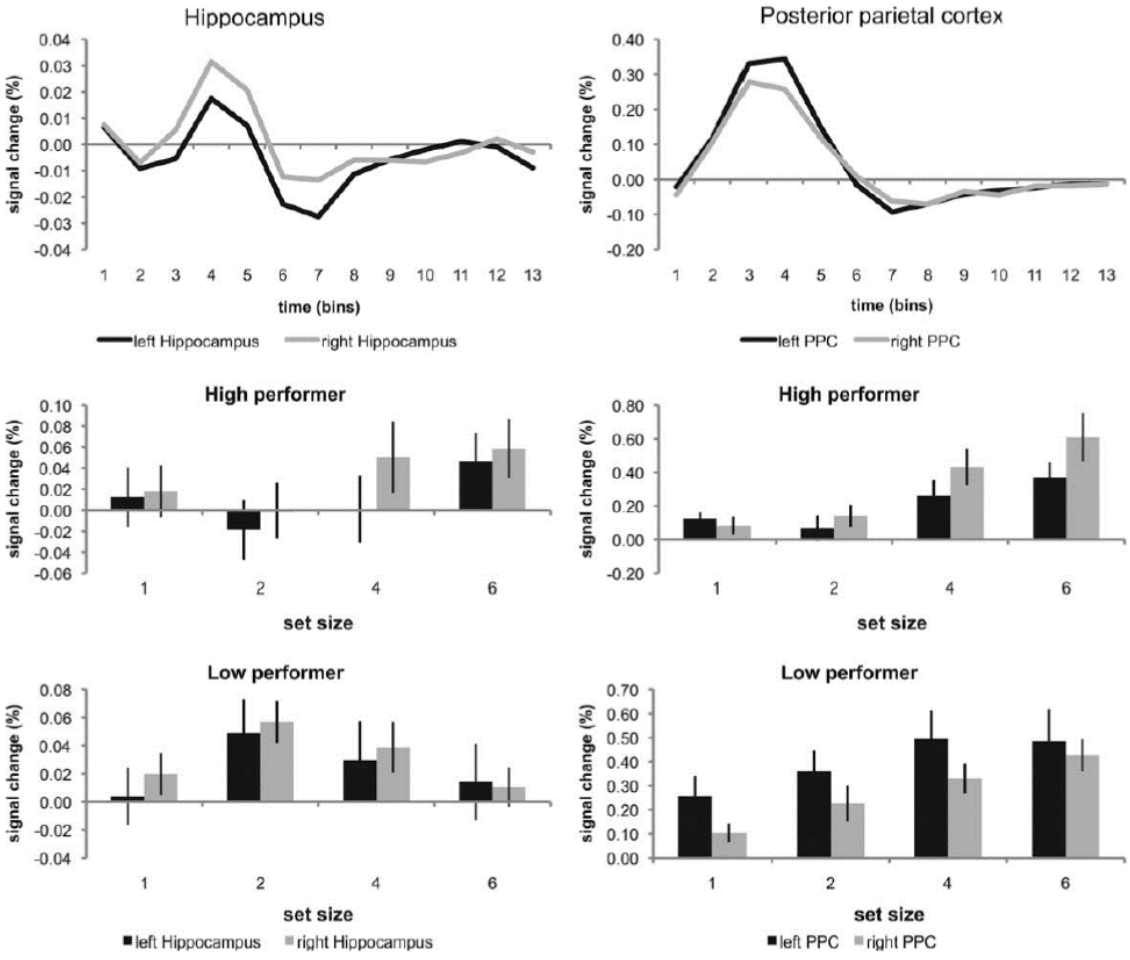

Figure 5.3. (top) Time courses for the left and right hippocampus and PPC, averaged over all conditions (0 – 24.7 seconds after sample onset). (bottom left) Left and right hippocampal activity for high and low performers at time bin 4. High performers showed increased neural activity at set size six. In low performers, hippocampal activity was maximally increased at set size two, followed by a reduction of activation with larger set sizes. Significant differences were found in high performers between set size six and two in the left hippocampus, and in low performers between set sizes two and six in the right hippocampus (post-hoc paired comparisons). (bottom right) PPC activity for high and low performers at time bins 3 and 4 (averaged percentage signal change). In both performance groups, PPC activity increased with larger set size. No significant 'set size x group' interaction was found.

5.5. Discussion

The current study investigated whether neural activity in the hippocampus and PPC related to individual VSTM performance. We found evidence that the hippocampus supported successful VSTM processing of object-location associations. Specifically, in our study, it seemed that set size-dependent activation in the hippocampus emerged within memory capacity and collapsed when capacity limit had been exceeded. With this, we provide evidence in support of unitary-store models, which postulate that short-term and long-term memory draw on the same neural structures.

Recent research on working memory representations using serial probe-recognition tasks (Nee & Jonides, 2008, 2011, 2013; Öztekin, Davachi, & McElree, 2010) are in line with our findings suggesting that the hippocampus supported processing of information within working memory capacity. These studies demonstrated that hippocampal activity was increased during probe-recognition for items classified to the active set, that is, information which is assumed to fall into the scope of the region of direct access (Oberauer, 2002). Moreover, the active set elicited increased hippocampal activity when individual working memory span was considered.

It has been alternatively argued that performance in a short-term memory task could in parts be supported by long-term memory, that is, the hippocampus is thought to contribute to task performance, when memory capacity has been exceeded (Jeneson & Squire, 2012; Jeneson et al., 2012). In our study, hippocampus activity was maximally enhanced at set sizes close to a performance group's mean K_{max}, which might indicate a hippocampus' engagement only when memory capacity had been reached. However, should hippocampus activity in our task have reflected long-term memory processes, this would have been accompanied by an increase of activity when capacity limit was exceeded. On the contrary, hippocampal activity in low performers dropped when capacity limit had been exceeded, which suggested that the hippocampus stopped being involved in successful VSTM processing. In this context, it should be noted that the mean K-score at set size six in low performers was in proximity to chance level. This implicates that object-location associations were not sufficiently processed when capacity limit was exceeded. We did not have the temporal resolution to disentangle encoding, maintenance and retrieval stages of VSTM processing. As hippocampal activity might contribute to all these stages of memory operations (Hannula & Ranganath, 2008; Piekema et

al., 2006; Toepper et al., 2010), impaired performance and reduced activity above capacity limits could be attributed to either memory formation deficits, forgetting or recognition failures. In high performers, an incremental set size-dependent increase in hippocampal activity might have reflected the larger number of object-location associations being processed. These findings are seemingly consistent with the view that VSTM capacity stems from a fixed number of objects available for processing. However, recent evidence supported that VSTM capacity is limited by both a fixed number of slots (e.g., Zhang and Luck, 2008) and a flexible pool of resources (e.g., Bays and Husain, 2008). The key for the engagement of one of these systems might be the type or scale of discernibility of multiple objects. Studies that found data compatible with slot accounts typically used objects of discrete features (e.g., objects of discrete colors and shapes), whereas evidence for flexible pools of resources were often found by comparing objects of continuous features difficult to categorize (e.g., objects of continuous shapes and color mixtures) (Diamantopoulou, Poom, Klaver, & Talsma, 2011; Olsson & Poom, 2005). As we used objects of distinct colors, we assume that VSTM capacity within our study was determined by a fixed number of objects.

As mentioned in the methods part, we forewent the use of K-weighted regressor coefficients to avoid missing brain activity which is not inherent to an underlying asymptotic function. Because an extreme groups approach (i.e., a division into high and low performers) might be a less powerful method to investigate neural activity associated with VSTM performance, we additionally probed set size-dependent activity by means of individual K_{max}-scores. Each subject's contrast between S_{max} and S1, and between S_{max} and S6 reflected an individual increase of neural activity until capacity limit had been reached, and an individual decrease of neural activity when capacity limit had been exceeded. This yielded equivalent findings as in the FIR analyses performed on the basis of an extreme groups approach.

In this study, although time course analyses were applied to delineate sample, delay and probe-related activity, and with respect to the short delay period used, one has to disregard a possible confound of encoding, maintenance and retrieval processes. To deal with that potential caveat, we performed whole brain- and FIR analyses with an extra factor of "probe" (match/mismatch), since one critical feature of the retrieval phase was that subjects had to make a match or mismatch decision. Neither of our analyses showed that match and mismatch trials were differently processed within the hippocampus other than in the PPC.

This could indicate that neural activity in the hippocampus was independent of the retrieval phase. Conversely, the PPC might have been involved in VSTM retrieval to a relatively greater degree. Further evidence might support this claim by varying the delay phase as performed by Todd and Marois (2005). But since our task was designed to furthermore examine children, we refrained from extending the study protocol. On balance, we cannot assume that hippocampal activity in our study was associated with a specific phase (i.e., encoding, maintenance, or retrieval). It rather summarizes performance-related activity during the whole working memory trial.

Regarding the delineation of different processes within a working memory trial, there is evidence that the hippocampus was involved in working memory encoding (Toepper et al., 2010), maintenance (Finke et al., 2008; Olson et al., 2006; Piekema et al., 2006), and retrieval (Hannula & Ranganath, 2008; Nee & Jonides, 2008, 2011; Öztekin et al., 2010; Öztekin, McElree, Staresina, & Davachi, 2008). Hence, the character or type of working memory representations seems to be critical for a hippocampal contribution, rather than the duration associated with a disjunct process (i.e., encoding, maintenance, or retrieval). With this in mind, our findings supported recent evidence that the hippocampus supported working memory for object-location processing (e.g., Piekema et al., 2006; Toepper et al., 2010). One could criticize that our experimental design did not control for spatial, nonspatial associations, and single items. However, it may be argued that our setup was sufficient to probe VSTM processing of object-location associations, since in our experiment the objects were trial-by-trial allocated at different places. A recent study used a similar task to probe VSTM for color-location associations (Finke et al., 2008). Within further conditions (i.e., color, and location only), they found no performance differences between patients with hippocampal lesions and healthy controls. Moreover, there is strong evidence that VSTM stores integrated objects rather than single features, not only within objects (Luck & Vogel, 1997), but also between objects and locations (Klaver et al., 1999). This suggests that whenever multiple objects with different locations are processed, VSTM stores integrated representations of object features including its spatial location.

In addition to the involvement of the hippocampus, we investigated whether the PPC contributed to successful VSTM performance, since previous imaging studies pointed to this region (e.g., Todd and Marois, 2004, 2005; Xu and Chun, 2006). Within whole brain analyses,

main effects of "set size" revealed strong activity in the PPC, but there was no evidence that PPC activity related to VSTM performance. A possible explanation could be that the number of trials per set size condition was kept low (20 trials per set size, further halved into match/mismatch conditions) due to reasons described in the methods part. By increasing the number of trials, one might have found a significant "set size x group" interaction within the PPC. Another reason can be derived from accounts claiming that PPC activity mirrored attentional processes during short-term memory processes (Bledowski et al., 2009; Jonides et al., 2008; Nee & Jonides, 2011). By extending the delay phase, one might have increased attentional demands (i.e., sustained attention) and evoked stronger engagement of the PPC.

In conclusion, both the hippocampus and the PPC might be differentially engaged during VSTM processing of object-location associations, depending on two processing types: object-location processing and attentional updating. Since we used rather short delay phases, attentional demands could have been diminished, while object-location processing emerged to be more critical. Most importantly, we suppose that, within our study, hippocampal activity reflected successful processing of object-location associations in the VSTM. With this, we do not only provide further neural evidence for unitary-store models, but also support existing views assuming that processing demands are crucial.

5.6. Acknowledgements

The authors like to thank Guillén Fernández for fruitful discussions and Ruth Tuura for technical support.

6. Study B

Hippocampal and posterior parietal contributions to developmental increases in visual short-term memory capacity

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Published in *Cortex*, DOI: 10.1016/j.cortex.2014.07.010 (accepted 24 July, 2014)

6.1. Abstract

Developmental increases in visual short-term memory (VSTM) capacity have been associated with changes in attention processing limitations and changes in neural activity within neural networks including the posterior parietal cortex (PPC). A growing body of evidence suggests that the hippocampus plays a role in VSTM, but it is unknown whether the hippocampus contributes to the capacity increase across development. We investigated the functional development of the hippocampus and PPC in 57 children, adolescents and adults (age 8-27 years) who performed a visuo-spatial change detection task. A negative relationship between age and VSTM related activity was found in the right posterior hippocampus that was paralleled by a positive age-activity relationship in the right PPC. In the posterior hippocampus, VSTM related activity predicted individual capacity in children, whereas neural activity in the right anterior hippocampus predicted individual capacity in adults. The findings provide first evidence that VSTM development is supported by an integrated neural network that involves hippocampal and posterior parietal regions.

6.2. Introduction

The amount of information that can be held in visual short-term memory (VSTM) is known to increase substantially from childhood through early adulthood (Gathercole, 1999; Pickering et al., 2001). The majority of evidence suggests that these improvements depend on changes in attention processing limitations and associated neural networks that include the posterior parietal cortex (PPC) (Klingberg et al., 2002; Klingberg, 2006; Olesen et al., 2003). These changes, however, do not serve as a sufficient explanation for age related capacity increases as suggested by behavioral and psychophysiological studies (Astle et al., 2014; Cowan et al., 2010). Instead, other cognitive processes and brain regions might additionally explain developmental improvements in VSTM capacity, which is to date unclear.

In the adult cognitive neuroscience literature, a growing body of research points to a role of the hippocampus in working memory (Finke et al., 2008; Hannula & Ranganath, 2008; Olson et al., 2006; Piekema et al., 2006). This idea was supported by recent evidence that neural activity in the hippocampus predicted individual VSTM capacity (von Allmen et al., 2013). In that study, participants performed a visuo-spatial change detection task during blood oxygenation level dependent (BOLD) fMRI scanning. In high capacity individuals, neural activity in the hippocampus incrementally increased up to set size six, whereas low capacity individuals showed a drop in hippocampal activity when their capacity limit had been exceeded. Within the present study, we aimed to substantiate our previous findings by testing the hippocampus' contribution to VSTM across development. In particular, we asked whether VSTM capacity is predicted by neural activity within the hippocampus across development and whether age related differences in hippocampal activity are linked to developmental increases in VSTM capacity.

In light of the development of the hippocampus, recent studies demonstrated age related structural and functional changes along its longitudinal axis (DeMaster & Ghetti, 2013; DeMaster, Pathman, Lee, & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Gogtay et al., 2006). Gogtay et al. (2006) for example reported developmental changes in gray matter volume along the hippocampal anterior-posterior axis, whereas its total volume remained constant. Furthermore, correct episodic retrieval of relational information in adults was associated with neural activity in the anterior hippocampus, whereas children showed the

same pattern specifically in the posterior hippocampus (DeMaster & Ghetti, 2013). Together, these findings provide evidence for regional age related changes in the hippocampus that might be as well related to simultaneously occurring progressive and regressive events along its longitudinal axis. Two further questions, therefore, were whether the anterior and posterior hippocampus show different developmental trajectories within the framework of VSTM and whether a possible regressive event in the posterior hippocampus parallels a progressive one in the anterior hippocampus with respect to a posterior-to-anterior shift.

In contrast to the sparse evidence for the role of the hippocampus in VSTM, it is well established that individual and developmental differences in VSTM capacity depend on neural activity in the PPC (Fukuda & Vogel, 2009; Klingberg et al., 2002; Magen et al., 2009; Olesen et al., 2007; Vogel et al., 2005). Another important question can hence be raised whether age related improvements in VSTM capacity may result from an integrated neural network that covers both the hippocampus and the PPC. In this context, we also intended to corroborate previous studies that reported age differences in working memory activity in the recruitment of the PPC (e.g., Klingberg et al., 2002).

In order to examine these questions, we measured BOLD fMRI in a priori defined subregions in the left/right hippocampus (head, anterior body, posterior body and tail) and PPC in three different age groups (children, adolescents and adults) during the completion of a visuo-spatial change detection task. Similar tasks have been used to probe set size modulated brain activity within VSTM (Todd & Marois, 2004; Vogel & Machizawa, 2004), or to demonstrate that damaged hippocampus affected processing of object-location associations (Finke et al., 2008; Olson et al., 2006).

6.3. Materials and Methods

6.3.1. Participants

Data were collected from 21 adults (age 19-27 years, mean = 22.2 ± 2.19 years, nine males), 16 adolescents (age 13-17 years, mean = 15.2 ± 1.47 years, six males) and 20 children (age 8-12 years, mean = 10.0 ± 1.34 years, nine males), after giving informed consent according to procedures approved by the Cantonal Ethics Committee Zurich. All participants were German speaking, had normal or corrected-to-normal vision and had no history of neuropsychiatric

disorders. Age groups were comparable in terms of their socioeconomic status (educational level of both parents) and did not differ in a common estimate of general nonverbal intelligence (Matrix Reasoning) and an assorted subtest for verbal intelligence (Similarities) that were assessed with the German versions of the Wechsler Intelligence Scale for Children (HAWIK-IV; Petermann and Petermann, 2007) and Wechsler Adult Intelligence Scale (WIE; Wechsler and von Aster, 2009) (data not shown). Additional data from seven children and three adolescents were excluded due to head motion during scanning that exceeded 3 mm, or because of failing to follow the instructions (one child). Within the adult group, we reanalyzed data of the same individuals previously examined (von Allmen et al., 2013).

6.3.2. Task Design

Before beginning the measurement, all participants were trained to perform the task on trials that were not included in the actual task. Fig. 6.1 (A) shows a sample of a trial used in our change detection task that required encoding, maintenance and retrieval of colored squares, spatially arranged within arrays of different set size conditions. Each trial started with a presentation of a central fixation cross on a light gray background (2000 ms). Then, an array of one, two, four or six objects was presented (800 ms). Subjects were instructed to retain these objects over a short period (900 ms). Finally, a probe array appeared (2000 ms), whereon subjects indicated by button press whether or not the probe matched the study array. A mismatch was introduced by a change of color in one square, while stimulus locations were held constant within a trial. Responses were given with index fingers of the left and right hand. Left-right allocation of response types (match/mismatch) was counterbalanced across subjects. Eighty trials in four set size conditions (20 trials per set size condition, 50% matches) and 24 null events (3500 ms, fixation cross) were randomly intermixed over the entire scanning session. Each trial onset was jittered with a variable inter-stimulus interval (8 x 0 ms, 6 x 1000 ms, 4 x 2000 ms and 2 x 3000 ms per set size condition).

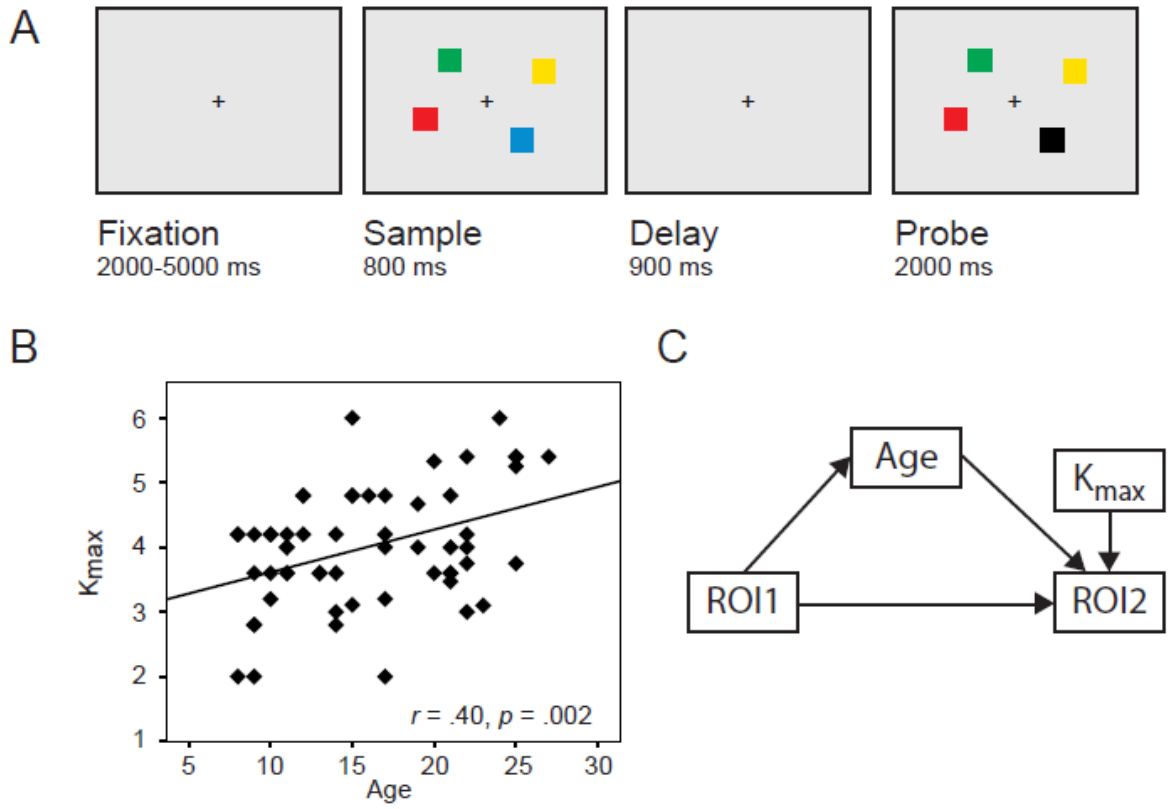

Figure 6.1. (A) Example of the visuo-spatial change detection task (mismatch trail). Participants were instructed to hold sample arrays consisting of one, two, four, or six colored squares for brief periods of time. By the presentation of the probe array, a match or mismatch response was required. (B) Correlation between age and K_{max} across the full developmental range. (C) Conceptual designs for the mediation model. The mediation analysis tested for a linear relationship between two regions (ROI1 and ROI2) mediated by age. Individual VSTM capacity was included as a covariate.

6.3.3. Image Acquisition

Whole brain functional images were acquired using conventional techniques on a 3-T GE MRI scanner (GE Medical Systems, Milwaukee, WI). Following four dummy scans, 354 T2*-weighted echo-planar imaging (EPI) scans were collected using an interleaved acquisition sequence (35 axial slices 15° to the AC-PC line, 3.13 x 3.13 mm^2 in plane, TR = 1.9 s, TE = 32 ms, 75° flip-angle, matrix = 64 x 64, slice thickness = 3 mm, slice gap = 0.3 mm). For task presentation, we used a Dell Precision M70 laptop running with Presentation 11 (Neurobehavioral Systems, Albany, CA) for Windows. The stimuli were back-projected on a screen viewed by the subject through a prism mirror.

6.3.4. fMRI Analysis

Functional MRI data were processed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London). All volumes were first corrected for slice acquisition timing and realigned to the first image for motion correction using rigid body realignment. Imaging data were then spatially normalized to the Montreal Neurological Institute (MNI) template brain (voxel size = 3 x 3 x 3). The use of a common adult template has been validated for children aged 7 years and older (Burgund et al., 2002; Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). To obtain hemodynamic response at stimulus onset for each event type, a canonical hemodynamic response function (HRF; Friston et al., 1998) and its temporal derivative were modelled. The events of interest were locked to the onset of sample arrays (duration = 3700 ms; onset sample array until end probe array). Four regressors modelled neural responses of the set size conditions. One additional regressor was used to model HRF related to incorrect trials (not considered in following statistical analyses) and additional 24 movement regressors were used to control for motion-correlated activity (implemented as multiple regressors within first level analyses). These included the standard 6 motion regressors, for translation (x, y and z) and for rotation (pitch, roll and yaw) with and without their temporal derivatives, plus their quadratic term with and without their temporal derivatives.

Regions of interest (ROI) analyses were performed with respect to our regional specific hypothesis regarding the hippocampus and PPC. Since evidence exists of developmental changes in the functional organization along the longitudinal axis of the hippocampus (DeMaster & Ghetti, 2013; Ghetti et al., 2010), we divided the left and right hippocampal ROI (provided by the AAL atlas) into eight non-overlapping subregions: left/right head, anterior body, posterior body and tail, using predefined Y-coordinates (DeMaster & Ghetti, 2013). A priori areas in the PPC were defined as spheres (radius = 8 mm) with the center at coordinates reported by Todd and Marois (2004) (left/right PPC, -22/23 -65/-59 42/45). We decided to adopt the coordinates from Todd and Marois due to the content related proximity to their approach. Percentage signal change estimates for each set size condition were extracted from the ROIs using MarsBar toolbox for SPM (Brett et al., 2002). Visual short-term memory related activity was operationalized as the activation difference between large (4 and 6) and small (1 and 2) set sizes ($S_{large} - S_{small}$). Within each ROI, a multiple regression analysis was performed in SPSS

22.0 (IBM, Armonk, NY) with the dependent variable $S_{large} - S_{small}$ and the factors age and K_{max}. The interaction term age*K_{max} was included as a third predictor.

6.4. Results

6.4.1. Behavioral Results

VSTM capacity was estimated by Cowan's K-formula (Cowan, 2001): K = (hit rate + correct rejection rate – 1) N, where N is the number of objects presented, by assigning the maximal K-score over all set size conditions (K_{max}). A hit was defined as a correctly identified mismatch. Across all 57 participants, K_{max} ranged from 2 to 6 objects (M = 4.01, SD = .92; detailed results are listed in Table 6.1). As expected, a positive correlation was found between age and K_{max} (r = .40, p = .002) (Fig. 6.1, B). In adults and adolescents, K_{max} correlated with hit rate at large set sizes (4 and 6) (adults, r = .71, p < .001; adolescents, r = .92, p < .001; children, r = .39, p = .092), while a similarly strong correlation between K_{max} and correct rejection rate at large set sizes was observed exclusively in children (children, r = .78, p < .001; adolescents, r = .54, p = .033; adults, r = .36, p = .106).

Table 6.1. VSTM capacity (K_{max}) across age groups.

	Mean Kmax ± SD	**MIN**	**MAX**
Adults	4.37 ± 0.90	3.00	6.00
Adolescents	3.91 ± 1.00	2.00	6.00
Children	3.71 ± 0.80	2.00	4.80

6.4.2. fMRI Results

The multiple regression analyses for each hippocampal ROI revealed a significant relationship between K_{max} and $S_{large} - S_{small}$ in the left and right hippocampal tail (left tail, β = .32, p = .024; right tail, β = .35, p = .012). As can be seen in Fig. 6.2 (A), $S_{large} - S_{small}$ in both of these regions ranged from negative in low capacity individuals to positive in high capacity individuals,

indicating a relative decrease in hippocampal activity at larger set sizes in low capacity individuals and a relative increase in hippocampal activity at larger set sizes in high capacity individuals.

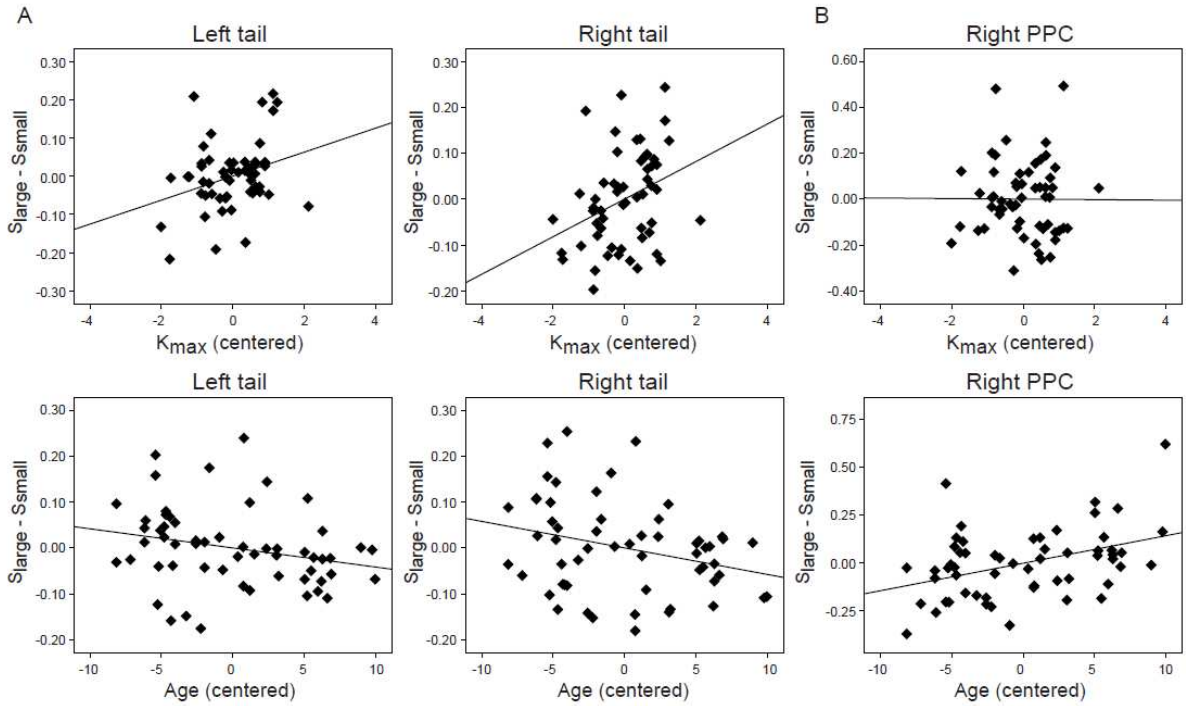

Figure 6.2. Linear relationships between $S_{large} - S_{small}$ and K_{max} (top) and age (bottom) for (A) the left and right hippocampal tail and (B) right PPC. For β and corresponding p-values, see Table 6.2.

To test for a hippocampal contribution to developmental improvements in VSTM capacity, we included age and age*K_{max} as further predictors within the regression models. This revealed a significant relationship between age and $S_{large} - S_{small}$ in the right hippocampal tail (β = -.30, p = .033). The negative direction of the regression coefficient indicates that VSTM related activity became smaller with increasing age (Fig. 6.2, A). Note that this linear relationship is independent of individual capacity and purely age related. Similarly, a trend to significance was found for a negative age-activity relationship in the left hippocampal tail (β = -.25, p = .070) (see also Table 6.2). Together, the data so far showed that a negative age-activity relationship in the posterior hippocampus was paralleled by a positive capacity-activity relationship in the same hippocampal subregion. The interaction term age*K_{max} was as well a significant predictor for $S_{large} - S_{small}$ in the left and right posterior hippocampus (left tail, β = -.26, p = .044; right tail, β = -.27, p = .034). To better understand these interaction effects, we

calculated post-hoc correlations between K_{max} and $S_{large} - S_{small}$ in the left and right hippocampal tail separately within each age group. This revealed a significant result only in children (left tail, $r = .69$, $p = .001$; right tail, $r = .75$, $p < .001$). Since in our previous study, individual capacity predicted VSTM related activity in bilateral anterior hippocampus (MNI coordinates for left/right hippocampus, -36/39 -16/-13 -17/-23) in adults (von Allmen et al., 2013), we calculated capacity-activity correlations for each age group in the left/right hippocampal head. This pointed to a significant result only in the adult's right head ($r = .55$, $p = .010$) (for detailed results, see supplementary information, Table A). In the right hippocampus, a functional specialization of the head was observed exclusively in adults, whereas children predominately recruited the tail during successful VSTM processing (Fig. 6.3).

Table 6.2. Multiple regression analyses within the hippocampal and posterior parietal ROIs.

	R^2		**Age**		**K_{max}**		**Age*K_{max}**	
$S_{large} - S_{small}$	R^2	p	β	p	β	p	β	p
Left hippocampus								
Head	.02	.783	-.10	.492	.12	.424	-.07	.599
Anterior body	.03	.642	-.11	.452	.04	.780	.15	.275
Posterior body	.02	.777	-.02	.890	.00	.980	-.14	.317
Tail	.16	.023	-.25	.070	.32	.024	-.26	.044
Right hippocampus								
Head	.01	.885	.02	.878	.08	.601	.05	.721
Anterior body	.02	.734	.01	.971	.13	.370	-.09	.497
Posterior body	.03	.623	.03	.817	.08	.589	-.17	.226
Tail	.20	.009	-.30	.033	.35	.012	-.27	.034
Left PPC	.05	.392	.22	.130	-.18	.223	-.06	.643
Right PPC	.19	.009	.44	.002	-.01	.965	-.15	.250

Listed are the regression coefficients (β) and its p-values for linear relationships between $S_{large} - S_{small}$ and the predictors age, K_{max} and age*K_{max}. The coefficient of multiple determination (R^2) and its p-value are as well listed.

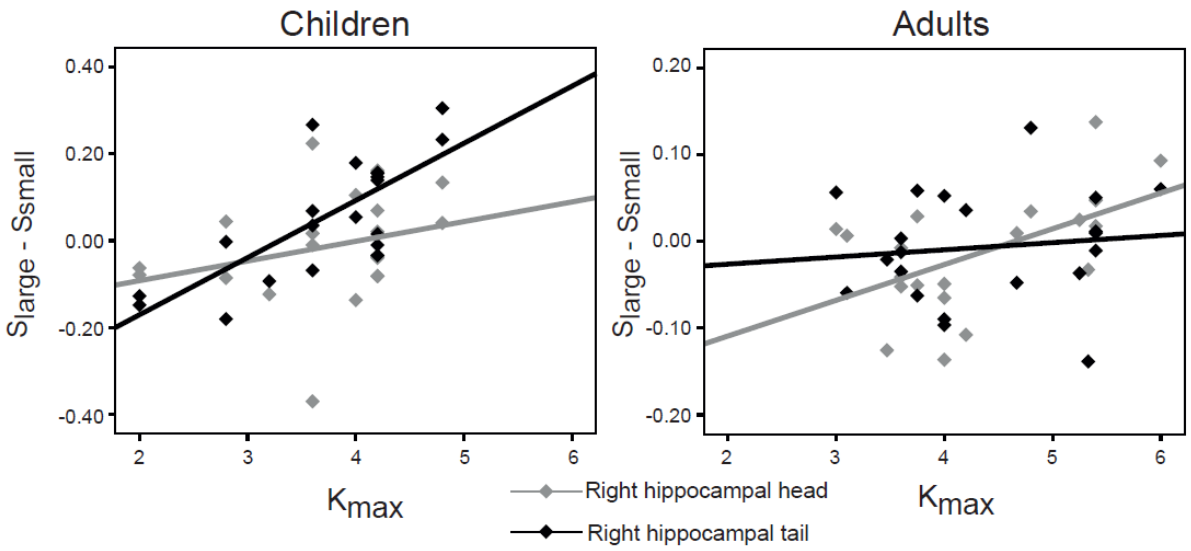

Figure 6.3. Correlations between K_{max} and $S_{large} - S_{small}$ in the right hippocampal head and tail for adults and children. For *r* and corresponding *p*-values, see Table A (supplementary information).

Due to developmental structural changes across the hippocampal longitudinal axis (Gogtay et al., 2006), our data might have depended on regional age related power differences. For that reason, we recalculated the regression analyses within each hippocampal ROI with an additional predictor of individual regional gray matter volume. Most importantly, regression coefficients and *p*-values for age, K_{max} and age*K_{max} did not markedly change in left and right hippocampal tail after holding individual differences in regional gray matter volume constant (see supplementary information, Table B).

In addition to the hippocampus, we investigated age related differences in the recruitment of the PPC. Two regression analyses (i.e., for the left/right PPC ROI) were conducted with the three predictors used above (age, K_{max} and age*K_{max}). Age was a significant predictor for $S_{large} - S_{small}$ in the right PPC ($\beta = .44$, $p = .002$). No reliable effects were found with respect to capacity related VSTM activity (i.e., K_{max} and age*K_{max} were no significant predictors for $S_{large} - S_{small}$, Table 6.2).

So far, neural activity increased with age in the right PPC and decreased with age in the right posterior hippocampus. In order to consolidate a potential hippocampus-to-PPC shift across development, we applied a more strict analysis, which tested for an inverse relationship between these two regions mediated by age using the INDIRECT macro for SPSS (www.afhayes.com). That is, we asked whether $S_{large} - S_{small}$ in the hippocampal tail (ROI1)

predicted $S_{large} - S_{small}$ in the PPC (ROI2) through the mediator age (a conceptual diagram is shown in Fig. 6.1, C). Because this test builds on the pure age related effects, which were independent of individual capacity, we included the covariate K_{max}. The same procedure was applied to additionally test for a head-to-PPC and a tail-to-head shift. To avoid power differences due to different ROI volumes (left/right PPC, 2240/2240 mm^2; head, 3728/3608 mm^2; tail, 1376/1528 mm^2), we defined the left/right anterior and posterior hippocampal ROIs as spheres with a radius of 8 mm (i.e., same radius as for the PPC sphere) at the center of mass of the original head and tail ROIs. No reliable effects were found for interregional relationships mediated by age. As can be seen in Table 6.3, $S_{large} - S_{small}$ in the left PPC inversely related to $S_{large} - S_{small}$ in the left hippocampal head ($\beta = -.49$, $p = .036$), which was independent of age (and K_{max}). Furthermore, the effect of $S_{large} - S_{small}$ in the right tail to age (path a) and the direct effect of age on $S_{large} - S_{small}$ in the right PPC (path b) were in line with the preceding findings.

Table 6.3. Linear relationships between $S_{large} - S_{small}$ in a given region (ROI1) and $S_{large} - S_{small}$ in another region (ROI2) with the mediator age and the covariate K_{max} (for a conceptual diagram, see Fig. 6.1, C).

	ROI1 to age (a)		**age to ROI2 (b)**		**ROI1 to ROI2 (c)**		**ROI1 to ROI2 (c')**	
$S_{large} - S_{small}$	β	p	β	p	β	p	β	p
Left hemisphere								
postHC-to- antHC	-17.8	.018	.00	.632	.19	.237	.17	.334
antHC-to-PPC	-5.32	.410	.01	.192	-.49	.036	-.46	.050
postHC-to-PPC	-17.8	.018	.01	.081	.15	.596	.31	.287
Right hemisphere								
postHC-to-antHC	-14.4	.048	.00	.498	.15	.317	.17	.255
antHC-to-PPC	2.71	.698	.01	.002	-.17	.483	-.21	.356
postHC-to-PPC	-14.4	.048	.01	.004	-.21	.419	-.01	.964

Listed are the unstandardized β-coefficients and p-values for ROI1 to age (path a), the direct effect of age on ROI2 (path b), the total effect of ROI1 on ROI2 (path c) and the direct effect of ROI1 on ROI2 (path c') (postHC = posterior hippocampal ROI, antHC = anterior hippocampal ROI, PPC = posterior parietal ROI).

6.5. Discussion

The present study aimed to investigate the neural bases of developmental improvements in VSTM capacity. Building on our previous study in adults (von Allmen et al., 2013), we first asked whether VSTM capacity related to hippocampal activity across the full developmental trajectory. We found a positive relationship between individual VSTM capacity and neural activity in bilateral posterior hippocampus. In particular, higher memory capacity was associated with a relative increase in neural activity at larger set sizes, while a decrease in activity was observed in low capacity individuals. In low capacity individuals, a drop in neural activity at larger set sizes suggests that the hippocampus stopped being involved in successful VSTM processing beyond capacity limit. This is in line with our previous study in adults (von Allmen et al., 2013) and contrasts with previous criticisms that hippocampal activity within short-term memory experiments actually emerged above capacity limit associated with long-term memory functions (Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012). Our findings therefore corroborate the view of a hippocampus' role in working memory (Finke et al., 2008; Hannula & Ranganath, 2008; Nee & Jonides, 2013; Olson et al., 2006; Piekema et al., 2006), i.e., by demonstrating its extent of validity for the first time across development.

The second question was whether age related differences in hippocampal activity were associated with developmental increases in VSTM capacity. Along with the positive capacity-activity relationship in bilateral hippocampal tail, we found a negative age-activity relationship in the right tail, suggesting that the role of the posterior hippocampus in successful VSTM processing becomes continuously less important with increasing age. Consistently, the interaction term age*K_{max} was a significant predictor for neural activity in this region. In other words, the positive relationship between individual capacity and neural activity was moderated by age, which further pointed to a strong capacity-activity correlation only in children. A posterior hippocampal involvement in successful VSTM processing thus was a particular feature in this age group. Unexpectedly, VSTM related activity in the anterior hippocampus was not predicted by age and individual capacity when tested linearly across the full developmental trajectory. However, when tested for a capacity-activity correlation separately within each age groups, individual capacity predicted neural activity in the right hippocampal head exclusively in adults, suggesting an anterior hippocampus' involvement in successful VSTM not before early adulthood. Together with the strong positive age-capacity

correlation, the current findings implicate a functional specialization in the adult anterior hippocampus associated with increased VSTM capacity and an initially predominant recruitment of the posterior hippocampus in childhood, which is in line with a recent study that showed a similar differentiation along the anterior-posterior axis of the hippocampus associated with differences in episodic retrieval between children and adults (DeMaster & Ghetti, 2013).

Regarding the involvement of the PPC in VSTM development, we found a positive age-activity relationship, which is in line with the existing developmental literature (Klingberg et al., 2002; Klingberg, 2006; Olesen et al., 2007). However, in contrast to for example Klingberg et al. (2002), our data did not show that an age-activity relationship in this region was paralleled with a capacity-activity relationship. There is substantial evidence that the PPC is specifically involved in VSTM when attentional processes are required (Bledowski, Rahm, & Rowe, 2009; Magen et al., 2009; Nee & Jonides, 2013). Hence, since our task was not designed to compare different levels of attentional demands, we refrain from further conclusions that an age related parietal contribution to VSTM is independent of individual capacity differences.

Development of working memory may be as well associated with a functional shift from the hippocampus to cortical regions, e.g., from the anterior hippocampus to prefrontal regions (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010). Because a negative age-activity relationship in the posterior hippocampus paralleled a positive one in the PPC, we probed whether these regions were inversely related to each other with respect to a possible developmental hippocampus-to-PPC shift. This analysis showed no reliable age-mediated interregional relationships, which could have further consolidated a functional shift from the posterior hippocampus to the PPC.

Do capacity and age related changes in activity within the hippocampus explain an age related increase in VSTM capacity? The current results showed that VSTM related activity in the right posterior hippocampus was not only negatively related to age but as well to individual capacity in children. In adults, individual VSTM capacity predicted neural activity in the anterior hippocampus. Neural activity in the anterior hippocampus has been associated with novelty processing (Düzel et al., 2003; Köhler, Danckert, Gati, & Menon, 2005; Pihlajamäki et al., 2004; Ranganath & D'Esposito, 2001; Sperling et al., 2001), whereas the posterior hippocampus was specifically involved in processing of spatial relations (Nadel,

Hoscheidt, & Ryan, 2012; Pihlajamäki et al., 2004). Both novelty detection and spatial processing play an important role in VSTM. First, according to the Feature Integration Theory (Wheeler & Treisman, 2002), whole-display recognition trials probe change detection (i.e., the detection of a novel item in a probe array), especially during the processing of object-location associations. Second, VSTM stores integrated representations of object features including their spatial locations and spatial relations (Bengson & Mangun, 2011; Klaver, Smid, & Heinze, 1999; Pertzov & Husain, 2013; Treisman & Zhang, 2006). We therefore suppose that the anterior hippocampal engagement might have reflected processing limitations in change detection abilities that seemed to gain in importance with increasing age for differentiating between high and low capacity individuals. Consistently, our data show a strong positive correlation between mean hit rate at larger set sizes and individual capacity in adults and adolescents. In contrast, individual differences in children's VSTM capacity might have predominantly relied on spatial processing limitations, which was paralleled by a strong positive correlation between mean correct rejection rate at larger set sizes and individual capacity. It is, however, important to note that since our task did not dissociate between novelty detection and spatial processing, first hand evidence will be required to substantiate our hypothesis of a functional dissociation between the anterior and posterior hippocampus.

To our knowledge, this is the first study to show that VSTM capacity is predicted by neural activity within the hippocampus across development. The data furthermore suggest a functional specialization of the anterior hippocampus by early adulthood, whereas children predominantly recruited the posterior part of the hippocampus during successful VSTM processing. The present study complements the widely acknowledged parietal contribution to working memory development by pointing to an additional involvement of the hippocampus.

6.6. Acknowledgements

We would like to thank Guillén Fernández and Ernst Martin for fruitful discussions, Ruth O'Gorman for technical support and the reviewers for their highly valuable and constructive comments.

6.7. Supplementary Information

Table 6.A. Correlations between $S_{large} - S_{small}$ and K_{max} within age groups.

	Adults		**Adolescents**		**Children**	
Region of Interest	*r*	*p*	*r*	*p*	*r*	*p*
Left hippocampus						
Head	.20	.380	-.14	.613	.20	.390
Tail	-.04	.869	.02	.945	.69	.001
Right hippocampus						
Head	.55	.010	-.38	.146	.28	.231
Tail	.12	.618	-.14	.599	.75	< .001

Table 6.B. Multiple regression analyses within the hippocampal ROIs controlled for individual gray matter volume.

	R^2		**Age**		K_{max}		**Age*K_{max}**		**GM**	
$S_{large} - S_{small}$	R^2	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Left hippocampus										
Head	.03	.844	-.06	.711	.13	.411	-.11	.456	-.11	.466
Anterior body	.07	.495	-.02	.886	.01	.941	.17	.230	.19	.204
Posterior body	.02	.902	.00	.985	.01	.966	-.14	.339	.01	.936
Tail	.17	.061	-.28	.065	.34	.026	-.26	.061	-.06	.672
Right hippocampus										
Head	.02	.916	.04	.813	.08	.620	.06	.687	.08	.581
Anterior body	.04	.786	.03	.832	.14	.388	-.11	.436	.08	.595
Posterior body	.07	.487	.06	.692	.12	.430	-.22	.147	-.17	.247
Tail	.22	.016	-.30	.039	.39	.008	-.29	.033	-.16	.237

Listed are the regression coefficients (β) and its *p*-values for linear relationships between $S_{large} - S_{small}$ and the predictors age, K_{max} and age*K_{max} and individual gray matter volume (GM). The coefficient of multiple determination (R^2) and its *p*-value are as well listed.

7. General Discussion

The goal of the present thesis was to investigate the following questions: whether neural activity in the hippocampus emerges below individual VSTM capacity not only in adults but also by middle childhood, whether neural activity in the hippocampus and PPC differentially explain individual and developmental differences in VSTM capacity, and whether age related regional changes along the hippocampal longitudinal axis explain developmental increases in VSTM capacity. For this purpose, we measured BOLD fMRI in three age groups (adults, adolescents, and children) while they performed a visuo-spatial change detection task. With respect to our regional specific hypothesis, a ROI analysis was performed over left/right parietal spheres and subregions along the hippocampal longitudinal axis.

7.1. Hippocampal Activity Emerges Below VSTM Capacity

Historically, the hippocampus is thought to be exclusively involved in long-term memory processes (Cohen et al., 1999; Squire et al., 1993). Recent accounts however indicated that the type of relational information determines the involvement of the hippocampus in memory processes rather than the time delay between encoding and retrieval (Henke, 2010; Ranganath & Blumenfeld, 2005). Alternatively, it has been suggested that within short-term memory tasks the hippocampus supported long-term memory processes particularly when memory capacity had been exceeded (Jeneson et al., 2012). According to that account, BOLD fMRI across set size conditions is predicted to arise when capacity limit has been exceeded, which is to date unclear.

Within our experiments, we directly probed below-capacity and above-capacity related hippocampal activity, not only in adults (**Study A**) but as well across development (**Study B**). The data revealed two main findings: In adults and children, neural activity in the hippocampus (1) predicted individual VSTM capacity, and (2) was differentially engaged across set size conditions. Regarding the latter finding, with the amount of successfully processed object-location associations, hippocampal activity incrementally increased and

dropped thereafter when capacity limit had been exceeded. To our surprise, neural activity in the hippocampus did not predict VSTM capacity in the adolescent group suggesting a non-linear developmental course of object-location processing in that region. Since most previous fMRI studies using the change detection paradigm mainly focused on specific types of relational information (Hannula & Ranganath, 2008; Piekema et al., 2006) without considering individual VSTM capacity, the present data substantially corroborate the view of a hippocampus' involvement in VSTM by demonstrating hippocampal activity exclusively below (and not above) an individual's capacity limit. The fact that these findings were replicable across adults and children indicates that VSTM capacity in these age groups was associated with comparable processes, namely the processing of object-location associations.

7.2. Differential Roles of the Hippocampus and PPC

While influential theories of working memory postulate a predominant role of attention and associated neural activity in the PPC within VSTM, there are some recent indications that attentional processing limitations might not be the whole story. The previous subsection outlined that hippocampal activity associated with memory related processing limitations might additionally explain individual capacity differences in adults and children. Within an integrated neural network, our next question was to determine whether neural activity in the hippocampus and PPC differentially explained individual and developmental differences in VSTM capacity. This would further provide evidence of two functionally dissociable components of VSTM capacity.

In contrast to the hippocampus, parietal activity did not predict individual VSTM capacity. Though, it can be stated that neural activity in this region increased with larger set size and leveled off beyond capacity limit which is in line with previous studies (Todd & Marois, 2004; Vogel & Machizawa, 2004). The differences between the hippocampus and PPC are therefore clear: Above-capacity related activity leveled off in the PPC and dropped in the hippocampus, which indicates that VSTM capacity results from dissociable neurocognitive mechanisms. As mentioned in the methods part, the Cowan's K-formula assumes that there is a likelihood of K/N on each trial that an observer correctly detects a change. The asymptotic shape of the K-function indicates that subjects are able to hold a fixed amount of information

that fits into their range of capacity irrespective whether set size exceeds capacity limit. Slot accounts furthermore claim a strong correlation between the K-function and VSTM related neural activity (Todd and Marois 2004, 2005; Vogel and Machizawa 2004). This seemingly contrasts with the observed activation drop in the hippocampus. An explanation for this discrepancy could be that below-capacity related performance benefited from hippocampal binding mechanisms. That is, hippocampal processing of object-location associations might have considerably improved performance as long as an array did not exceed memory capacity. Beyond capacity limit, however, object-location associations might have fallen apart, while compensatory mechanisms in the PPC sustained to furthermore support performance without benefiting from the hippocampus.

A clear dissociation between the hippocampus and PPC was furthermore observed across the developmental trajectory. More specifically, age related improvements in VSTM capacity were driven by linear changes in the PPC, while the hippocampus showed a regional specialization towards its anterior part across development. Linear developmental courses in attention related activity in the PPC are well known in the literature (Klingberg et al., 2002), while the neural substrates of developmental improvements in object-location processing are yet unknown.

Here, it should be states that this thesis does not assume completely independent processes regarding attentional and memory related operations. Most influential theories of working memory propose that VSTM capacity is primarily determined by attentional processing limitations (Cowan, 1999; McElree, 2006; Oberauer, 2002). Furthermore, it is well established that working memory binding is substantially biased by attention (Chou & Yeh, 2012; Chun, 2011; Derek E. Nee & Jonides, 2013). It should be however considered that the hippocampus might provide a kind of relational workbench in which relations can be temporarily held or processed. Along with the significant influence of attention, this hippocampal workbench may have its limits as well, which might be understood as memory-related.

7.3. Age-Related Regional Changes in the Hippocampus

Previous findings support the idea of a structural specialization along the longitudinal axis of the hippocampus from childhood through early adulthood (Gogtay et al., 2006). Furthermore, these age-related changes in the hippocampus have been associated with developmental improvements in episodic memory retrieval for relational information (DeMaster & Ghetti, 2013; Ghetti et al., 2010). Based on these findings, we asked whether developmental increases in VSTM capacity are linked to age-related changes along the hippocampal longitudinal axis.

The analyses revealed that individual VSTM capacity in adults related to neural activity in the right anterior hippocampus, whereas a posterior hippocampal involvement seemed to be a particular feature in children. Moreover, in the children's right anterior hippocampus, neural activity was associated with an increase in VSTM capacity with age. These findings clearly indicate a functional specialization towards the anterior part of the hippocampus and provide for the first time neural evidence for qualitative age related changes in object-location processing across the developmental trajectory.

7.4. Limitations

Within our studies, we used a whole-display recognition approach to probe VSTM object-location processing. Capacity limit was estimated by the Cowan's K-Formula (Cowan, 2001): K = (hit rate – false alarm rate) x N. It has been most recently suggested that this function is specifically suited for single-probe recognition (Rouder, Morey, Morey, & Cowan, 2011). These authors furthermore suggest that for whole-display recognition K-scores should be calculated by means of the formula provided by Pashler (1988): K = (hit rate – false alarm rate) / (1 – false alarm rate) x N. It should be however highlighted that performance groups do not change by a subsequent capacity estimation with the Pashler's formula, neither do the correlational findings of the fMRI data.

A challenge relevant for many fMRI studies is that the coupling ratio between CBF and cerebral metabolic rate of oxygen ($CMRO_2$) can substantially vary across the cerebral cortex, which ideally ranges from 2 to 4.5 (i.e., the higher that ratio, the more reliable a coupling between positive BOLD signal and neural activity can be assumed) (Chiarelli et al., 2007;

Leontiev, Dubowitz, & Buxton, 2007). However, a recent study demonstrated that the hippocampus is associated with a lower coupling ratio of about 1.7 (Restom, Perthen, & Liu, 2008), most probably because of the relatively poor vascular supply compared to the cerebral cortex (Borowsky & Collins, 1989). Low coupling ratio limits the interpretability of neural activity in the hippocampus, especially when observing deactivation. That is, a deactivation can emerge from at least three possibilities when blood supply is poor: (1) both CBF and $CMRO_2$ decline, (2) $CMRO_2$ remains constant, while CBF is drawn off by regions significantly involved in an ongoing task, and (3) $CMRO_2$ exceeds CBF. While the first interpretation would be supported by our intuition, the latter two should be as well considered as possible causes for hippocampal deactivation. In light of our studies, the observed hippocampal deactivation in the adult low performer's hippocampus at set sizes four and six are thus indeed ambiguous. Keeping this in mind, one should treat this particular case of deactivation with caution.

Especially when analyzing data within a developmental fMRI study, one should be aware of task-irrelevant differences in the BOLD response between adults and children. Specifically, CBF directly affects the BOLD response which is known to differ markedly across development with a peak during middle childhood (Takahashi, Shirane, Sato, & Yoshimoto, 1999; Wintermark et al., 2004), which go in parallel with synaptic pruning mechanisms and increases in gray matter volume (Giedd et al., 1999; Huttenlocher, 1990). With this in mind, it is not surprising that children generally showed higher BOLD signal in the hippocampus compared to adults particularly at higher set size conditions. We assume that our core findings and conclusions regarding the hippocampus are not affected by age related BOLD differences. That is, VSTM capacity related hippocampal activity was determined within age groups. Secondly, children and adults showed similar hippocampal activation patterns across set size conditions which may indicate comparable processes over development. However, it cannot be excluded that capacity related parietal activity across development might have been affected by such changes in BOLD response, since these effects were only observed when testing across the entire developmental trajectory.

7.5. Conclusion and Outlook

Most importantly, we found that VSTM related activity in the hippocampus emerged below an individual's capacity limit in both children and adults, whereas different subregions along the longitudinal axis predicted individual VSTM capacity in these age groups. In addition, neural activity in the PPC showed strong capacity related effects across the entire developmental trajectory. To corroborate the idea that VSTM capacity across development results from both attention and memory related processing limitation, future work should provide direct evidence that the hippocampus and PPC are functionally dissociable. Another question concerns the hippocampal anterior-posterior dissociation across VSTM development, namely whether or how distinct binding mechanisms can functionally dissociate the anterior from the posterior hippocampus.

8. References

Allen, R. J., Baddeley, A. D., & Hitch, G. J. (2006). Is the binding of visual features in working memory resource-demanding? *Journal of Experimental Psychology: General*, *135*(2), 298–313.

Astle, D. E., Harvey, H., Stokes, M., Mohseni, H., Nobre, A. C., & Scerif, G. (2014). Distinct neural mechanisms of individual and developmental differences in VSTM capacity. *Developmental Psychobiology*, *56*(4), 601–610.

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proceedings of the National Academy of Sciences*, *107*(7), 3228–3233.

Axmacher, N., Mormann, F., Fernández, G., Cohen, M. X., Elger, C. E., & Fell, J. (2007). Sustained neural activity patterns during working memory in the human medial temporal lobe. *The Journal of Neuroscience*, *27*(29), 7807–7816.

Bays, P. M., & Husain, M. (2008). Dynamic shifts of limited working memory resources in human vision. *Science*, *321*(5890), 851–854.

Benes, F. M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophrenia Bulletin*, *15*(4), 585–593.

Bengson, J. J., & Mangun, G. R. (2011). Individual working memory capacity is uniquely correlated with feature-based attention when combined with spatial attention. *Attention, Perception, & Psychophysics*, *73*(1), 86–102.

Bledowski, C., Rahm, B., & Rowe, J. B. (2009). What "works" in working memory? Separate systems for selection and updating of critical information. *The Journal of Neuroscience*, *29*(43), 13735–13741.

Borowsky, I. W., & Collins, R. C. (1989). Metabolic anatomy of brain: A comparison of regional capillary density, glucose metabolism, and enzyme activities. *The Journal of Comparative Neurology*, *288*(3), 401–413.

Brett, M., Anton, J., Valabregue, R., & Poline, J. (2002). Region of interest analysis using an SPM toolbox. *NeuroImage*, *16*(2).

Buckner, R. L., Koutstaal, W., Schacter, D. L., Dale, A. M., Rotte, M., & Rosen, B. R. (1998). Functional–anatomic study of episodic retrieval: II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. *NeuroImage*, *7*(3), 163–175.

Bull, R., Espy, K. A., & Wiebe, S. A. (2008). Short-term memory, working memory, and executive functioning in preschoolers: Longitudinal predictors of mathematical achievement at age 7 years. *Developmental Neuropsychology*, *33*(3), 205–228.

Burgund, E. D., Kang, H. C., Kelly, J. E., Buckner, R. L., Snyder, A. Z., Petersen, S. E., & Schlaggar, B. L. (2002). The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *NeuroImage*, *17*(1), 184–200.

Cabeza, R., Dolcos, F., Graham, R., & Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *NeuroImage*, *16*(2), 317–330.

Cave, C. B., & Squire, L. R. (1992). Intact verbal and nonverbal short-term memory following damage to the human hippocampus. *Hippocampus*, *2*(2), 151–163.

Chiarelli, P. A., Bulte, D. P., Gallichan, D., Piechnik, S. K., Wise, R., & Jezzard, P. (2007). Flow-metabolism coupling in human visual, motor, and supplementary motor areas assessed by magnetic resonance imaging. *Magnetic Resonance in Medicine*, *57*(3), 538–547.

Chou, W.-L., & Yeh, S.-L. (2012). Object-based attention occurs regardless of object awareness. *Psychonomic Bulletin & Review*, *19*(2), 225–231.

Chun, M. M. (2011). Visual working memory as visual attention sustained internally over time. *Neuropsychologia*, *49*(6), 1407–1409.

Cohen, N. J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., & Nash, C. (1999). Hippocampal system and declarative (relational) memory: Summarizing the data from functional neuroimaging studies. *Hippocampus*, *9*(1), 83–98.

Conway, A. R. A. (2008). *Variation in working memory*. New York, NY, US: Oxford University Press.

Cowan, N. (1999). An embedded-processes model of working memory. In *Models of working memory*. Cambridge University Press.

Cowan, N. (2001). The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *The Behavioral and Brain Sciences*, *24*(1), 87–114; discussion 114–185.

Cowan, N., Morey, C. C., AuBuchon, A. M., Zwilling, C. E., & Gilchrist, A. L. (2010). Seven-year-olds allocate attention like adults unless working memory is overloaded. *Developmental Science*, *13*(1), 120–133.

Cowan, N., Naveh-Benjamin, M., Kilb, A., & Saults, J. S. (2006). Life-span development of visual working memory: When is feature binding difficult? *Developmental Psychology*, *42*(6), 1089–1102.

DeMaster, D. M., & Ghetti, S. (2013). Developmental differences in hippocampal and cortical contributions to episodic retrieval. *Cortex*, *49*(6), 1482–1493.

DeMaster, D. M., Pathman, T., Lee, J. K., & Ghetti, S. (2013). Structural development of the hippocampus and episodic memory: Developmental differences along the anterior/posterior axis. *Cerebral Cortex*.

Diamantopoulou, S., Poom, L., Klaver, P., & Talsma, D. (2011). Visual working memory capacity and stimulus categories: a behavioral and electrophysiological investigation. *Experimental Brain Research*, *209*(4), 501–513.

Fell, J., Dietl, T., Grunwald, T., Kurthen, M., Klaver, P., Trautner, P., Schaller, C., Elger, C. E., & Fernández, G. (2004). Neural bases of cognitive ERPs: More than phase reset. *Journal of Cognitive Neuroscience*, *16*(9), 1595–1604.

Fiacconi, C. M., & Milliken, B. (2013). Visual memory for feature bindings: The disruptive effect of responding to new perceptual input. *The Quarterly Journal of Experimental Psychology*, *0*(0), 1–29.

Finke, C., Braun, M., Ostendorf, F., Lehmann, T.-N., Hoffmann, K.-T., Kopp, U., & Ploner, C. J. (2008). The human hippocampal formation mediates short-term memory of colour–location associations. *Neuropsychologia*, *46*(2), 614–623.

Finn, A. S., Sheridan, M. A., Kam, C. L. H., Hinshaw, S., & D'Esposito, M. (2010). Longitudinal evidence for functional specialization of the neural circuit supporting working memory in the human brain. *The Journal of Neuroscience*, *30*(33), 11062–11067.

Fougnie, D., & Marois, R. (2009). Attentive tracking disrupts feature binding in visual working memory. *Visual Cognition*, *17*(1-2), 48–66.

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences*, *83*(4), 1140–1144.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., & Turner, R. (1998). Event-related fMRI: Characterizing differential responses. *NeuroImage*, *7*(1), 30–40.

Fukuda, K., & Vogel, E. K. (2009). Human variation in overriding attentional capture. *The Journal of Neuroscience*, *29*(27), 8726–8733.

Fukuda, K., Vogel, E., Mayr, U., & Awh, E. (2010). Quantity, not quality: the relationship between fluid intelligence and working memory capacity. *Psychonomic Bulletin & Review*, *17*(5), 673–679.

Gathercole, S. E. (1999). Cognitive approaches to the development of short-term memory. *Trends in Cognitive Sciences*, *3*(11), 410–419.

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1), 1–16.

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., & Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *The Journal of Neuroscience*, *30*(28), 9548–9556.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–863.

Giovanello, K. S., Schnyer, D., & Verfaellie, M. (2009). Distinct hippocampal regions make unique contributions to relational memory. *Hippocampus*, *19*(2), 111–117.

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., Clasen, L., Toga, A. W., Giedd, J. N., Rapoport, J. L., & Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus*, *16*(8), 664–672.

Hannula, D. E., & Ranganath, C. (2008). Medial temporal lobe activity predicts successful relational memory binding. *The Journal of Neuroscience*, *28*(1), 116–124.

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience*, *11*(7), 523–532.

Huttenlocher, P. R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia*, *28*(6), 517–527.

Jäncke, L. (2005). *Methoden der Bildgebung in der Psychologie und den kognitiven Neurowissenschaften*. Stuttgart: Kohlhammer.

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory*, *19*(1), 15–25.

Jeneson, A., Wixted, J. T., Hopkins, R. O., & Squire, L. R. (2012). Visual working memory capacity and the medial temporal lobe. *The Journal of Neuroscience*, *32*(10), 3584–3589.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Moore, K. S. (2008). The mind and brain of short-term memory. *Annual Review of Psychology*, *59*(1), 193–224.

Kahneman, D., Treisman, A., & Gibbs, B. J. (1992). The reviewing of object files: Object-specific integration of information. *Cognitive Psychology*, *24*(2), 175–219.

Kang, H. C., Burgund, E. D., Lugar, H. M., Petersen, S. E., & Schlaggar, B. L. (2003). Comparison of functional activation foci in children and adults using a common stereotactic space. *NeuroImage*, *19*(1), 16–28.

Klaver, P., Smid, H. G. O. ., & Heinze, H.-J. (1999). Representations in human visual short-term memory: an event-related brain potential study. *Neuroscience Letters*, *268*(2), 65–68.

Klingberg, T. (2006). Development of a superior frontal–intraparietal network for visuo-spatial working memory. *Neuropsychologia*, *44*(11), 2171–2177.

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *Journal of Cognitive Neuroscience*, *14*(1), 1–10.

Leontiev, O., Dubowitz, D. J., & Buxton, R. B. (2007). CBF/CMRO2 coupling measured with calibrated BOLD fMRI: Sources of bias. *NeuroImage*, *36*(4), 1110–1122.

Lorsbach, T. C., & Reimer, J. F. (2005). Feature binding in children and young adults. *The Journal of Genetic Psychology*, *166*(3), 313–328.

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*(6657), 279–281.

Magen, H., Emmanouil, T.-A., McMains, S. A., Kastner, S., & Treisman, A. (2009). Attentional demands predict short-term memory load response in posterior parietal cortex. *Neuropsychologia*, *47*(8–9), 1790–1798.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*, *19*(3), 1233–1239.

McElree, B. (2006). Accessing recent events. In *Psychology of Learning and Motivation* (Vol. 46, pp. 155–200). Elsevier.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterizing the hemodynamic response: Effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage*, *11*(6), 735–759.

Mitchell, K. J., Johnson, M. K., Raye, C. L., & D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. *Cognitive Brain Research*, *10*(1–2), 197–206.

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233.

Nee, D. E., & Jonides, J. (2008). Neural correlates of access to short-term memory. *Proceedings of the National Academy of Sciences*, *105*(37), 14228–14233.

Nee, D. E., & Jonides, J. (2011). Dissociable contributions of prefrontal cortex and the hippocampus to short-term memory: Evidence for a 3-state model of memory. *NeuroImage*, *54*(2), 1540–1548.

Nee, D. E., & Jonides, J. (2013). Neural evidence for a 3-state model of visual short-term memory. *NeuroImage*, *74*, 1–11.

Nee, D. E., & Jonides, J. (2013). Trisecting representational states in short-term memory. *Frontiers in Human Neuroscience, 26*(*7)*, 796.

Oberauer, K. (2002). Access to information in working memory: exploring the focus of attention. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *28*(3), 411–421.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, *87*(24), 9868–9872.

Olesen, P. J., Macoveanu, J., Tegnér, J., & Klingberg, T. (2007). Brain activity related to working memory and distraction in children and adults. *Cerebral Cortex*, *17*(5), 1047–1054.

Olesen, P. J., Nagy, Z., Westerberg, H., & Klingberg, T. (2003). Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research*, *18*(1), 48–57.

Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., & Verfaellie, M. (2006). Working memory for conjunctions relies on the medial temporal lobe. *The Journal of Neuroscience*, *26*(17), 4596–4601.

Olsson, H., & Poom, L. (2005). Visual memory needs categories. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(24), 8776–8780.

Öztekin, I., Davachi, L., & McElree, B. (2010). Are representations in working memory distinct from representations in long-term memory? Neural evidence in support of a single store. *Psychological Science*, *21*(8), 1123–1133.

Öztekin, I., McElree, B., Staresina, B. P., & Davachi, L. (2008). Working memory retrieval: Contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. *Journal of Cognitive Neuroscience*, *21*(3), 581–593.

Pashler, H. (1988). Familiarity and visual change detection. *Perception & Psychophysics*, *44*(4), 369–378.

Paz-Alonso, P. M., Ghetti, S., Donohue, S. E., Goodman, G. S., & Bunge, S. A. (2008). Neurodevelopmental correlates of true and false recognition. *Cerebral Cortex*, *18*(9), 2208–2216.

Pertzov, Y., & Husain, M. (2013). The privileged role of location in visual working memory. *Attention, Perception & Psychophysics*.

Petermann, F., & Petermann, U. (2007). *Hamburg-Wechsler-Intelligenztest für Kinder - IV*. Bern: Huber.

Phillips, W. A. (1974). On the distinction between sensory storage and short-term visual memory. *Perception & Psychophysics*, *16*(2), 283–290.

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., & Piolino, P. (2012). How do the different components of episodic memory develop? Role of executive functions and short-term feature-binding abilities. *Child Development*, *83*(3), 1037–1050.

Pickering, S. J., Gathercole, S. E., Hall, M., & Lloyd, S. A. (2001). Development of memory for pattern and path: further evidence for the fractionation of visuo-spatial memory. *The*

Quarterly Journal of Experimental Psychology. A, Human Experimental Psychology, *54*(2), 397–420.

Piekema, C., Kessels, R. P. C., Mars, R. B., Petersson, K. M., & Fernández, G. (2006). The right hippocampus participates in short-term memory maintenance of object–location associations. *NeuroImage*, *33*(1), 374–382.

Ranganath, C., & Blumenfeld, R. S. (2005). Doubts about double dissociations between short- and long-term memory. *Trends in Cognitive Sciences*, *9*(8), 374–380.

Ranganath, C., & D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. *Neuron*, *31*(5), 865–873.

Restom, K., Perthen, J. E., & Liu, T. T. (2008). Calibrated fMRI in the medial temporal lobe during a memory-encoding task. *NeuroImage*, *40*(4), 1495–1502.

Riggs, K. J., Simpson, A., & Potts, T. (2011). The development of visual short-term memory for multifeature items during middle childhood. *Journal of Experimental Child Psychology*, *108*(4), 802–809.

Rouder, J. N., Morey, R. D., Morey, C. C., & Cowan, N. (2011). How to measure working memory capacity in the change detection paradigm. *Psychonomic Bulletin & Review*, *18*(2), 324–330.

Schon, K., Hasselmo, M. E., LoPresti, M. L., Tricarico, M. D., & Stern, C. E. (2004). Persistence of parahippocampal representation in the absence of stimulus input enhances long-term encoding: A functional magnetic resonance imaging study of subsequent memory after a delayed match-to-sample task. *The Journal of Neuroscience*, *24*(49), 11088–11097.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, *20*(1), 11–21.

Simmering, V. R., Johnson, J. S., Patterson, C. M., & Spencer, J. P. (2009). When objects disintegrate: Young children do not bind features in visual working memory. In *Proceedings of the Thirty-First Annual Conference of the Cognitive Science Society, Cognitive Science Society, Amsterdam*, 106–111.

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology*, *33*(1), 5–42.

Squire, L. R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory. *Annual Review of Psychology*, *44*(1), 453–495.

Stern, C. E., Sherman, S. J., Kirchhoff, B. A., & Hasselmo, M. E. (2001). Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. *Hippocampus*, *11*(4), 337–346.

Takahashi, T., Shirane, R., Sato, S., & Yoshimoto, T. (1999). Developmental changes of cerebral blood flow and oxygen metabolism in children. *American Journal of Neuroradiology*, *20*(5), 917–922.

Thomason, M. E., Burrows, B. E., Gabrieli, J. D. E., & Glover, G. H. (2005). Breath holding reveals differences in fMRI BOLD signal in children and adults. *NeuroImage*, *25*(3), 824–837.

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754.

Todd, J. J., & Marois, R. (2005). Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognitive, Affective & Behavioral Neuroscience*, *5*(2), 144–155.

Toepper, M., Markowitsch, H. J., Gebhardt, H., Beblo, T., Thomas, C., Gallhofer, B., Driessen, M., & Sammer, G. (2010). Hippocampal involvement in working memory encoding of changing locations: An fMRI study. *Brain Research*, *1354*, 91–99.

Treisman, A., & Zhang, W. (2006). Location and binding in visual working memory. *Memory & Cognition*, *34*(8), 1704–1719.

Vogel, E. K., & Machizawa, M. G. (2004). Neural activity predicts individual differences in visual working memory capacity. *Nature*, *428*(6984), 748–751.

Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature*, *438*(7067), 500–503.

von Allmen, D. Y., Wurmitzer, K., Martin, E., & Klaver, P. (2013). Neural activity in the hippocampus predicts individual visual short-term memory capacity. *Hippocampus*, *23*(7), 606–615.

Wechsler, D., & von Aster, M. (Eds.). (2009). *Wechsler Intelligenztest für Erwachsene* (2., korr. Aufl.). Frankfurt/M.: Pearson Assessment.

Wheeler, M. E., & Treisman, A. M. (2002). Binding in short-term visual memory. *Journal of Experimental Psychology. General*, *131*(1), 48–64.

Wintermark, M., Lepori, D., Cotting, J., Roulet, E., van Melle, G., Meuli, R., Maeder, P., Regli, L., Verdun, F. R., Deonna, T., Schnyder, P., & Gudinchet, F. (2004). Brain perfusion in

children: Evolution with age assessed by quantitative perfusion computed tomography. *Pediatrics*, *113*(6), 1642–1652.

Xu, Y., & Chun, M. M. (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature*, *440*(7080), 91–95.

Zeithamova, D., & Preston, A. R. (2010). Flexible Memories: Differential Roles for Medial Temporal Lobe and Prefrontal Cortex in Cross-Episode Binding. *The Journal of Neuroscience*, *30*(44), 14676–14684.

Zhang, W., & Luck, S. J. (2008). Discrete fixed-resolution representations in visual working memory. *Nature*, *453*(7192), 233–235.

Curriculum Vitae

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Education and Qualifications

2010 – 2014	Ph.D. student at the University of Zurich, Switzerland. Ph.D. thesis title: "Neurocognitive Factors Underpinning Individual and Developmental Differences in Visual Short-Term Memory Capacity" Supervisors: PD Peter Klaver, Ph.D., Prof. Ernst Martin, M.D., Prof. Andreas Maercker, Ph.D. / M.D.
2002 – 2008	MSc in Psychology at the University of Zurich, Switzerland. Master thesis title: "Eine EEG Studie zu den Verarbeitungs-prozessen im primären visuellen Kortex". Supervisor: Valentine Marcar, Ph.D.
2001 – 2002	Studies of Mechanical and Process Engineering at the ETH Zurich, Switzerland.
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Research Experience

01/2010 – 11/2013	Research Fellow University Children's Hospital Zurich Swiss National Science Foundation (SNF) sponsored study Study title: "Common neural mechanisms of working memory and episodic memory in typical and atypical development".
01/2013 – 10/2013	Research Assistant University Clinics for Child and Adolescent Psychiatry
02/2010 – 07/2011	Tutor Chair of Psychopathology and Clinical Intervention Department of Psychology, University of Zurich
05/2006 – 09/2006	Student apprentice University Hospital of Psychiatry Zurich
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Other Professional Experience

02/2009 – 12/2009	Therapist Integrierte Psychiatrie Winterthur, Winterthur
06/2004 – 05/2009	Employee Swiss library for the visually impaired, Zurich

Peer-Reviewed Publications

von Allmen David Yoh, Wurmitzer Karoline, Martin Ernst, & Klaver Peter (2013). Neural activity in the hippocampus predicts individual visual short-term memory capacity. *Hippocampus*, *23*(7), 606–615.

von Allmen David Yoh, Wurmitzer Karoline, & Klaver Peter. Hippocampal and posterior parietal contributions to developmental increases in visual short-term memory capacity. *Cortex*, accepted.

Congress Posters / Presentations

von Allmen David Yoh, Wurmitzer Karoline, Martin Ernst, & Klaver Peter (2012). "A hippocampal-parietal network differentially supports visual short-term memory: A developmental imaging approach". Poster presented at: Annual meeting Neuroscience , New Orleans (LA / USA).

von Allmen David Yoh, Wurmitzer Karoline, Martin Ernst, & Klaver Peter (2012). "The hippocampus and posterior parietal cortex: Two interacting brain regions during maintenance". Poster presented at: Memory Slam, Amsterdam (NL).

von Allmen David Yoh, Wurmitzer Karoline, Martin Ernst, & Klaver Peter (2012). "Right hippocampal activity predicts performance in short-term maintenance of object-location associations". Poster presented at: Zurich Neuroscience Center (ZNZ) Symposium, Zurich (CH).

von Allmen David Yoh (2011). "Typical and atypical development of memory: An fMRI Study". Oral presenation at: Research retreat of the Forschungszentrum für das Kind (FZK), Au (CH).

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